1971

THE IMPACT OF THE NATIONAL CANCER ACT

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DEPARTMENT OF HEALTH AND HUMAN SERVICES • Public Health Service • National Institutes of Health

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Foreword

The National Cancer Act of 1971, signed into law by President Richard M. Nixon on December 23,1971, expanded and intensified the nation's cancer research and control program. The framers of the Act believed that biomedical research conducted in the 1950s and 1960s had produced results that should be exploited for the benefit of cancer patients and the general public. They convinced Congress and the President that the infusion of substantial additional resources would not only allow cancer investigators to follow-up the clues and leads generated by earlier research, but that research findings would be sped more rapidly to the aid of health professionals, cancer patients, and individuals at risk of cancer.

Recognizing that the 20th anniversary of the Act would be an appropriate occasion to informally assess the impact of the legislation, the *Journal of the National Cancer Institute's* News Section published 25 articles contrasting knowledge, practice, or attitudes toward cancer in 1971 with that of 1991. This series of articles began in the December 19, 1990 issue of the Journal and ended in the December 18, 1991 issue.

Because of the interest generated by the series, the *Journal* is reprinting the articles under one cover.

J. Paul Van Nevel
Editor, News Section
Journal of the National Cancer Institute

The 1971 National Cancer Act—Did It Pay Off?

By Cori Vanchieri

The National Cancer Act was passed in 1971 to give cancer research and control a much needed infusion of energy, authority, and dollars. Expectations were high. Legislators called for cures for the major forms of cancer in time for the nation's bicentennial—1976.

Some cures have been discovered, others remain elusive, but there is agreement among the nation's top researchers that without the Act, today's biomedical revolution would still be a pipe dream.

"The cancer program is the viable, progressive, result-producing effort of today because of the focus provided by the National Cancer Act," said Armand Hammer, M.D., chairman of the President's Cancer Panel.

President Richard M. Nixon, who signed the National Cancer Act into law, has called the Act one of the most significant actions taken during his administration. He placed it on par with his historic trip to China, the first U.S.-Soviet nuclear arms limitation agreements, and the reduction of forces in Vietnam.

President Nixon signs the National Cancer Act—1971.

Funding Slump

The push for greater support for cancer research was initiated for two reasons: (1) recent discoveries had opened up promising areas of investigation that required an expanded research program; and (2) funding for the National Institutes of Health in the late 1960s had slowed substantially, causing some to proclaim that federal support of research was losing ground.

The President's budget request for NCI in 1970 was 2% below the 1969 appropriation. In calling for a report on the status of cancer research, Ralph W. Yarborough, then a Texas senator who chaired the Senate Committee on

The National Cancer Act Provided Special Authorities

In 1970, Senator Ralph W. Yarborough, who was chairman of the Senate Labor and Public Welfare Committee, called for a study of the status of cancer research.

The resulting National Panel of Consultants on the Conquest of Cancer, cochaired by Benno Schmidt and Sidney Farber, M.D., developed a report called, "A National Program for the Conquest of Cancer." This report was the blueprint for the development of the National Cancer Act, which provided NCI with special authorities to coordinate, expand, and expedite cancer research.

These special authorities made the NCI director a presidential appointee, created the President's Cancer Panel, and allowed NCI to submit a "bypass" budget directly to the President. Although the commission originally suggested taking NCI out of the National Institutes of Health, the final legislation kept NCI within NIH.

President Richard M. Nixon signed the National Cancer Act on December 23, 1971. Nixon had shown the extent of his support of the cancer effort when, in January 1971, he requested an extra $100 million for NCI for fiscal year 1972. That increased NCI's budget from $230 million in FY 1971 to $379 million in FY 1972. The FY 1973 budget rose to $492 million.

NCAB Established

The National Cancer Act established the National Cancer Advisory Board, whose 18 scientific and lay members are appointed by the President. All major initiatives that affect the institute or the cancer program are first brought to the NCAB for advice and guidance.

The bypass budget allows the institute to submit its budget directly to the President without change by the NIH or the Department of Health and Human Services. This bypass budget clarifies the level of funding that is necessary to conduct cancer research and control efforts and establishes priorities for those projects.

With the bypass budget, "Congress has a window on the full spectrum of views, which it doesn't always get when presented in the more orderly fashion [through DHHS]," Schmidt said.

"The essence of the Cancer Act was to provide not only more resources for cancer research, which it did, but some protection from the bureaucratic processes that tend to envelop special initiatives," said Vincent T. DeVita, Jr., M.D., NCI's director from 1980 to 1988.

The protection came with "special authorities to allow the institute to operate with greater speed and flexibility, and special reporting lines to troubleshoot problems that might arise," he added. DeVita is now at Memorial Sloan-Kettering Cancer Center, New York.

"The signs of the scientific revolution around us are undeniable, and much of it was fueled by funds provided to and programs initiated by the National Cancer Program," DeVita added.

The National Cancer Act has been reauthorized six times, each time with added directives, including those on information dissemination, prevention, and technology transfer. The current reauthorization is pending.

Labor and Public Welfare, noted that the government spent only $200 million for cancer research in 1970. More than that was spent by Americans on ball point pens, and nearly twice as much was spent on chewing gum, he said. At Yarborough's behest, a group of businessmen, scientists, and cancer advocates began devising a plan to garner attention and support for cancer research. The group was called the National Panel of Consultants on the Conquest of Cancer, or more informally, the Yarborough Commission.

The best way to expand cancer research, the commission reasoned, was to provide special authorities and funding to the National Cancer Institute. (See boxed story on the previous page.)

Their plan was the basis for the National Cancer Act.

But not everyone was sold on the idea of giving NCI special authorities and extra funding.

"The toughest part was developing an understanding in the scientific community of what we really had in mind doing," said Benno Schmidt, cochair of the commission.

Many were afraid that the framers of the Act were trying to target applied research on cancer before a scientific base was developed.

The Main Point

But, according to Schmidt, the main point of the Act was "to accelerate and expand the effort in basic biomedical research to try to learn at the cellular and molecular level what is going on in these chronic diseases, which take up a primary portion of our medical agenda."

Others feared that too much money would go to cancer centers and not enough to the universities where equally good basic research was being done.

Still others feared that peer review would be diluted, damaging the quality of research. All of these concerns came to be unfounded. Finally, a number were afraid that any increased appropriation to NCI would result in a decrease to other institutes.

"We counted heavily on the assumption that as NCI's budget increased, the other institute budgets would similarly increase. That's exactly what happened," Schmidt said.

Budgets Grew

During the 1970s, the NIH budget increased at the same rate as the NCI budget—the NIH budget went from $1 billion in 1971 to $3.5 billion in 1980 and the NCI budget rose from $230 million in 1971 to more than $1 billion in 1980. In the 1980s, the NIH budget increased more rapidly than the NCI budget. By 1990, the NIH budget reached $7.6 billion while the NCI budget hit $1.6 billion.

"The National Cancer Act is responsible for the fact that the NIH budget has moved from about $1 billion to over $7 billion today," Schmidt said. During the same time, contributions to the American Cancer Society also have increased—from $70 million in 1971 to $350 million in 1989.

Originally Wary

One scientist who was originally wary of the Act is Paul Marks, M.D., president of Memorial Sloan-Kettering Cancer Center, New York. Marks wrote to Schmidt explaining his concerns.

"I was worried that a program focused on cancer would distort a national effort in support of biomedical research as a whole," he said. Marks said he was eventually convinced of the benefits of the Act when he saw that the cancer program was supporting good fundamental research and that the developers understood the value of peer review to allocate resources. He is now a firm supporter.

"Products of the National Cancer Act were not just good for cancer, but also for our whole effort in viral disease," he said.

"Without [the Act], we would've been totally unprepared for subsequent problems—like AIDS," Marks continued. "The speed with which AIDS etiology was determined is clearly a product of work in cancer."

Private industry has picked up on the poten-

tial for discoveries in molecular and genetic research as well as their clinical applications. "Happily, a great deal of private money is now being spent in the further development in these fields of biomedical research that were opened up by the marvelous fundamental basic research done in the 1970s and 1980s," Schmidt said.

National Cancer Program Develops

1971

1971 —National Cancer Act signed by President Nixon on December 23

1973 —First eight Comprehensive Cancer Centers recognized
—Surveillance, Epidemiology and End Results (SEER) Program established

1974 —NCI made first cancer control awards to state health departments
—Clinical Cancer Education Program began

1975 —Extramural Cancer Cooperative Clinical Trials Program added to Division of Cancer Treatment

1976—Cancer Information Service (CIS) opened

1981

1981 —Biological Response Modifiers Program established

1982 —PDQ (Physician Data Query) made available nationwide

1983 —Community Clinical Oncology Program launched
—Chemoprevention branch established

1984 —Cancer Prevention Awareness Program launched

1988 —First Clinical Alert released
—First Consortium Cancer Center comprised of three historically black medical schools established

1989 —World's largest demonstration project for tobacco control—ASSIST—began

1990 —NCI's automated human cell line drug screening system made fully operational

1991

1991 —Twentieth Anniversary of the National Cancer Act marked

More To Do

While noting the progress that has been achieved, Senator Edward Kennedy (D-MA), who many consider one of the strongest and most abiding sources of congressional support for the Act, sees a need to look toward the future.

Recognizing that the achievements afforded by the National Cancer Act touched many families, Kennedy noted that his son Teddy would not be alive today without the improvements made in cancer research and treatment.

"Every day in every city across the country, citizens are being helped by this progress," Kennedy said. "I intend to do all I can to see that it continues."

Many believe that a new infusion of support will be necessary to keep the discoveries coming.

"[The Act] gave the impetus to many other disease groups to get involved and get more support and resources for medical research," said Terry Lierman, president of the National Coalition for Cancer Research, a coalition of cancer research, cancer care, and advocacy groups.

As a result, other groups have become more visible on Capitol Hill. The cancer community, which was very vocal during passage of the Act, has slacked off in its aggressiveness, he said.

His sentiments are echoed by Mary Lasker, whose "Lasker Lobby" was a driving force behind the instigation and passage of the 1971 Act.

"The National Cancer Act . . . has worked well in many areas—but what we must all do is recommit ourselves to finding the final answers," Lasker said.

Lierman said he has recently seen a re-involvement of the scientific and lay community to get cancer back on the national agenda.

New Technologies Profoundly Change Cancer Research

By Jill Waalen

In the 20 years since the signing of the National Cancer Act, biological research has undergone a technological revolution unequaled in its history.

The techniques that sparked the revolution—recombinant DNA, which allows manipulation of individual genes, and hybridomas, which produce high-fidelity monoclonal antibodies—have profoundly changed cancer research and opened the way to new modes of diagnosis and treatment undreamed of in 1971.

Theoretical Constructs

In the wake of these technological breakthroughs, oncogenes, theoretical constructs when proposed by Robert Huebner, M.D., and George Todaro, M.D., in 1969, have materialized, with more than 50 human oncogenes now identified.

Finding oncogenes and suppressor genes and their protein products using these tools has been pivotal in cancer research. "The progress has been monumental," said Alan S. Rabson, M.D., director of the National Cancer Institute's Division of Cancer Biology, Diagnosis, and Centers.

"[In 1971], people had a hunch that cancer was a genetic disease. By finding the genes, we are now able to figure out how they are damaged in the disease process and develop strategies to intervene in the process," he said.

The progress since the inception of biotechnology in the mid-1970s is especially remarkable considering the bleak situation faced by scientists studying cancer cell genetics in 1971.

Evidence that cancer is a disease rooted in altered genes was mounting, but researchers had no way to isolate these genes. Family studies and inbred mice with a propensity for tumors had shown some cancers to be heritable.

Studies with hybrid cells, created by fusing human malignant cells with normal mouse cells and containing chromosomes from each, had suggested that cancer was caused by a genetic factor capable of being suppressed.

Additionally, DNA tumor viruses were known to insert their DNA into host cell chromosomes. The discovery in 1970 of reverse transcriptase, an enzyme that copies RNA back into DNA, suggested RNA tumor viruses did the same, further evidence for the existence of cancer-causing genes.

But while the double helix structure of the DNA molecule had been unveiled 18 years before, and its triplet code directing protein synthesis deciphered for a decade, the genes buried within the DNA of chromosomes could not be isolated in 1971.

Further progress awaited a method of breaking the huge chromosomes down into manageable chunks for identification and sequencing of individual genes—a problem that was not solved until the discovery of enzymes that recognize specific sequences.

Had No Idea

"I don't think anyone at the time had any idea we could even do molecular genetics," Rabson said.

The lack of tools limited the areas of research. Some researchers focused on transfer RNA molecules, short chains of nucleotides that could be sequenced with the nonspecific enzymes then available.

The premise was that a change in a few nucleotides could change a transfer RNA molecule's preference for a particular amino acid and result in malfunctioning proteins that may trigger tumorigenesis. A 1971 review article in *Cancer Research* even suggested that "all carcinogenesis might be due to alterations of minor bases of transfer RNA."

At the same time, chromosome banding techniques were heralded as "an entirely new approach" to investigating whether portions of chromosomes were missing, displaced, reversed, or repeated in tumor cells, a concept inspired by the discovery of the Philadelphia chromosome associated with chronic lymphocytic leukemia.

Some molecular biologists used electron microscopes for a closer view of chromosomal DNA. By adding electron-scattering bases, they hoped to "see" nucleotide sequences.

Barriers Overcome

The technological barriers were finally overcome by the discovery of restriction endonucleases, enzymes that stranded DNA at specific nucleotide sequences. The fact that some restriction enzymes leave single-stranded tails at the ends of the clipped DNA could be exploited, allowing DNA fragments to recombine with other DNA fragments clipped by the same enzyme.

Dr. Stanley Cohen

Thus, pieces of DNA from eukaryotic cells can be inserted into bacterial chromosomes treated by the same restriction enzyme. As the bacteria divide, they copy the inserted DNA along with their own DNA. Hence, a gene can be cloned, a technique first described by Stanley Cohen, M.D., Herbert Boyer, Ph.D., and colleagues in 1973.

Other technological advances soon followed recombinant DNA. In 1975-1976, two methods were devised independently by Frederick Sanger, Ph.D., and by the team of Walter Gilbert, Ph.D., and Allan Maxam, Ph.D., to sequence restriction fragments.

Southern Blot

In 1975, E.M. Southern, Ph.D., applied electrophoresis to separate DNA fragments resulting from a restriction enzyme digest, distributing the fragments within a gel according to size.

With sequences in hand, probes made of complementary strands of DNA or RNA could be constructed to radioactively tag fragments of interest in the bands of a Southern blot.

At about the same time, monoclonal antibody technology emerged, a spinoff of the cell hybridization techniques being used to study malignant cells. In 1975, Cesar Milstein, Ph.D., and Georges Koehler, Ph.D., fused antibody-producing B cells from a mouse with human cancer cells to create a hybridoma. The B-cell hybrids were then cloned to produce only one type of antibody, a monoclonal.

Since then, monoclonal antibodies have become molecular workhorses, employed to identify myriad biologically active proteins, including protein products of isolated genes.

The new recombinant DNA and monoclonal antibody technologies quickly spawned a whole new industry, with the first biotech company, Genentech, founded in 1976.

In the 1980s, two new techniques further accelerated the identification of genes and mapping of genes. Because distinct genes are difficult to identify and isolate, fragments produced by restriction enzymes have been used as chromosomal landmarks.

Scientists have found that some base changes, or polymorphisms, in these fragments are associated with mutations in neighboring

genes. Thus, so-called restriction fragment length polymorphisms (RFLP) can indicate gene mutations without having to isolate the gene.

RFLP application to cancer research is widespread, most recently reported in some colon and breast cancers.

PCR

The latest addition to the biotech repertoire is the polymerase chain reaction (PCR). The method makes millions of copies of a particular DNA fragment, starting with only minute amounts of the DNA to be copied, primer sequences, nucleotides, and a DNA polymerase. By bypassing biological vectors, PCR cuts the time needed to clone DNA fragments from several weeks to a few hours. Developed in the mid-1980s, PCR has caught on fast. "Every major molecular biology lab is using it now," said Ira Pastan, M.D., chief of NCI's Laboratory of Molecular Biology.

Today biotechnology is an integral part of new cancer treatments designed to fix genes and arm cells with powerful and specific anti-tumor agents, with the application to patients unfolding before our eyes.

Radiolabeled monoclonal antibodies confirm that this patient's cutaneous T-cell lymph cancer involves the lymph nodes and skin. The antibodies collect in the cancerous lymph nodes of the armpits. neck, and groin, and a strong outline of the patient's body verifies skin involvement. The liver and spleen are darkened, too, because it is normal for these organs to collect the antibodies.

Gene Therapy

The first human gene therapy study began last September when NCI investigators R. Michael Blaese, M.D., and Kenneth W. Culver, M.D., and W. French Anderson, M.D., of the National Heart, Lung, and Blood Institute, added the human ADA gene to the white blood cells of a patient with adenosine deaminase deficiency.

In 1991, gene therapy for melanoma will be under way. The protocol, developed by Steven A. Rosenberg, M.D., Ph.D., chief of NCI's Surgery Branch, equips lymphocytes with a gene for a tumor toxin, tumor necrosis factor, inserted into the cells' genome by a disabled virus.

Other types of gene therapies will emerge as the products of oncogenes are identified, Pastan said. For example, Pastan is studying an oncogene known to code for a growth receptor.

He and his colleagues plan to attack the receptor with a genetically engineered growth hormone with an oncotoxin attached. When the toxin-carrying growth hormone binds to the receptor on the tumor cell, the toxin will destroy it.

In the same way, monoclonal antibodies targeted for specific tumor antigens are being armed with radioactive or toxic molecules designed to kill tumor cells. Radioactive monoclonals have long been used as diagnostic tools as well.

With such tools at hand, the possibilities for cancer research and treatment seem limitless, and the technological barriers faced in 1971, increasingly remote.

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1971-1991: Science Unlocks Cancer Cell Secrets

By Patricia A. Newman

"The nature of cancer is not yet fully known . . . . We must learn more about what takes place at the cellular level when cancer occurs."

With these words, some 20 years ago, the introduction to the landmark report of the National Panel of Consultants on the Conquest of Cancer encouraged expansion of basic research on cancer.

The Panel, also called the Yarborough Commission because it had been created by then-Senator Ralph W. Yarborough, developed the blueprint for the National Cancer Act of 1971. The Act expanded and intensified cancer research in the United States.

Two decades later, the explosion of knowledge from ensuing years of cancer research is mind-boggling, even for scientists.

Belief Now Proven

In 1970, scientists believed cancer to be the result of a multistep process. By 1990, they had proven this theory beyond doubt.

A great deal is now known about molecular events in cancer, and new information is being reported daily. The surprise has been that even within a cell, cancerous changes can occur by a variety of routes.

It is now clear that inside the cell, cancer development and progression are driven by mutations resulting in defective cell proliferation and differentiation.

What is not yet clear, except for one or two cancers, is exactly what these defects are, how they are induced by environmental exposures, and why they often appear to be tissue specific.

For the field of molecular biology, the Yarborough Commission report correctly predicted that "cancer, whatever its causes, clearly involves a dysfunction at the molecular level in the cellular control mechanisms. Basic research in the molecular biology of cancer is the area of investigation most likely to reveal this fundamental underlying disorder."

Merged Then Branched

Findings in cancer virology and molecular biology merged during the 1970s, then branched out into highly specialized disciplines during the 1980s as scientists studying viral and normal genes followed separate leads.

While it was clear that viruses containing reverse transcriptase used it to make a DNA copy of the RNA genome, which then was incorporated into the genes of the host cell, viruses were not widely believed to play a major role in most human cancers.

And, many scientists began to suspect that, until they understood normal cell functions, they would not be able to pinpoint the molecular pathways that culminated in cancer.

Today, research on oncogenes is providing information on one of the most fundamental

puzzles in biology: how cells know when to divide. The research has equally fundamental implications for cancer, because cancer cells often contain activating mutations in proto-oncogenes or loss of gene functions.

"The whole phenomenon of oncogenes and suppressor genes is the single most important thing to come out of cancer research in any decade," said Frank J. Rauscher, Jr., Ph.D, former National Cancer Institute director and former American Cancer Society senior vice president for research.

Motivated

In 1970, basic scientists found themselves motivated by the intriguing discovery by Howard Temin, Ph.D., and David Baltimore, Ph.D., of the enzyme named RNA-dependent DNA polymerase, or reverse transcriptase.

"We didn't even know about oncogenes at that time," said Rauscher. "We now recognize 50 or more, and they're probably related to most of the diseases that we call cancer one way or the other, either by deletion or loss of a controlling gene, or the masking of a controlling gene."

Rauscher said that scientists used to say that "cancer is essentially an extrinsically induced disease. People don't get cancer because they're people; they get cancer because of something they do, they eat, they drink, they smoke, to some extent where they work and live. Now with the oncogene phenomenon . . . clearly these genes are intrinsic." Nonetheless, their activation as oncogenes is due to something extrinsic, according to Rauscher.

It is becoming more and more apparent, he said, that the extrinsic factor will probably not be carcinogenic without "the turning on of something that people are born with. Simply the recognition of that is probably more important than anything that has ever come out of cancer research."

1970 Thinking

In 1970, scientists thought retroviruses caused cancer in animals in a single step. After infecting a cell, they thought, the virus used reverse transcriptase to make a DNA copy of the viral RNA, the viral DNA integrated into cellular DNA, and the viral parasite thereafter produced progeny using the cell's genetic machinery.

Then the discovery of recombinant DNA technology in the 1970s made it possible for scientists to manipulate specific gene sequences and led to a massive effort to dissect their structure and function.

Cancer research benefited along with other disease fields: In 1976, J. Michael Bishop, M.D., and Harold E. Varmus, M.D., discovered the first oncogene in a certain retrovirus. This gene, which could convert normal cells to cancer, was in fact a modified cellular gene.

Later work showed that these mutant genes are derived from cellular genes called proto-oncogenes. Now, scientists know that the proto-oncogenes are members of families of genes that control cell growth and differentiation. Virtually all cancer cells show some type of chromosomal rearrangement, some relatively specific for particular cancers. Some oncogene activation occurs by chromosomal translocation.

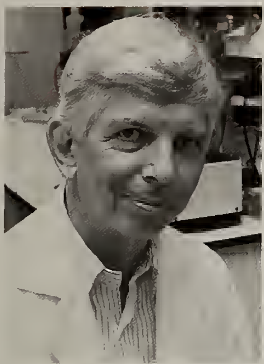
Best Examples

The best-known examples are Burkitt's lymphoma and chronic myelogenous leukemia, where activation occurs when an oncogene translocates during cell division to a position in a daughter cell on another chromosome near a proto-oncogene. This results in deregulation of the oncogene, and cancer occurs.

In a few cases, chromosomal aberrations occur in inherited cancers. One of the best-known examples is retinoblastoma.

In 1971, Alfred G. Knudson, Jr., M.D., Ph.D., of the Fox Chase Cancer Center in Philadelphia, proposed a two-hit carcinogenesis mechanism that suggested that retinoblastoma arose when both copies of a single gene were inactivated.

These dual mutations subsequently were identified, and the target gene cloned. The retinoblastoma (RB) gene acts as a tumor sup-



Dr. Alfred G. Knudson

pressor in a dominant fashion: as long as one normal copy of the gene is present, the cell is normal, but loss of both normal copies leads to cancer.

An altered or deleted RB gene has now been identified in some osteosarcomas, soft tissue sarcomas, ductal breast carcinomas, small-cell lung cancers, and bladder and prostate cancers.

However, retinoblastoma is the only cancer known where deletion of just one gene results in cancer. In the other cancers, the development of the disease process appears to require additional DNA damage.

Li-Fraumeni Syndrome

In recent years, the *p53* gene has been found mutated in a variety of cancers. Using a screening test based on polymerase chain reaction technology, scientists from the National Cancer Institute and the Dana Farber Cancer Institute recently reported inheritance of a mutated *p53* gene in Li-Fraumeni syndrome, an inherited cancer syndrome.

The *RB* and *p53* genes are now the targets of intense scrutiny to understand their role in human cancers. Like the *RB* gene, the *p53* gene is believed to be needed for normal cell growth.

Loss or mutation of *p53* appears to be one of several DNA mutations that occur in colon cancer. Understanding the gene's role in colon cancer may lead to a better understanding of other cancers as well.

Scientists recently also have found a connection between the proto-oncogenes and the activity of human viruses believed to play an important role in human cervical cancers. In laboratory tests, the proteins encoded by both *RB* and *p53* can attach to the E6 and E7 proteins of two "high-risk" human papillomaviruses found in the DNA of human cervical cancer cells.

By attaching to normal proteins like p53 and RB, which are needed for normal cell division, the viral proteins may be inactivating them, thus increasing the possibility of abnormal cell division.

Progress in Defining

"We have made tremendous progress in defining what a cancer cell is all about, and one of the main reasons is that we tied in to the cell cycle," said George Vande Woude, Ph.D., director of the ABL Basic Research Program at the NCI Frederick Cancer Research and Development Center, Frederick, Md.

Duplication of DNA and partitioning of that DNA to progeny cells are two key events in the cell cycle where oncogenes, proto-oncogenes, and tumor suppressor genes may be functioning.

"You have classes of genes that regulate duplication and classes of genes that regulate the movement of duplicated DNA into progeny cells. And, along the way, there are signals, pauses in the process, that say, 'OK, everything is correct, move forward.'" In cancer cells, this regulation is altered and the process probably moves forward without appropriate corrections.

The research is leading to new models for how oncogenes might be causing cancer, Vande Woude said.

The research is also leading to a fresh look at how successful cancer drugs work, some of which appear to be active during duplication of DNA and some during partitioning. "We're beginning to see the light at the end of the tunnel," Vande Woude said.

"But," he added, "We are not far enough along to know that it is a light and not an oncoming train."

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Cancer Prevention: Out of the Shadows and Into the Cell

By Kara Smigel

In the 20 years since the passage of the National Cancer Act, science has changed both the basic concepts of cancer causation and national strategies to prevent the disease.

Frank J. Rauscher, Jr., Ph.D., then director of the National Cancer Institute, said in 1972 that "cancer develops because of something a person does, because of the way he lives, or because of something he's exposed to."

Since then, cancer prevention strategies have progressed from the identification and avoidance of carcinogens to include sophisticated biochemical manipulation of the carcinogenic process. As researchers learned the mechanics of carcinogenesis, new pathways to prevention became clear.

Cancer Causers

Identification of carcinogens was hardly a standardized affair as late as 1965. Individual laboratories ran small series of animal tests on chemicals, usually industrial substances, on an "as needed" basis. What one laboratory called a carcinogen might not be a carcinogen by another lab's standards.

An NCI project to standardize the identification of carcinogens was at the point of application when the National Panel of Consultants on the Conquest of Cancer (whose work led to the National Cancer Act) reported on the needs of cancer research. A combination of public concern and good timing put the newly created carcinogen bioassay program into the limelight.

"After the National Cancer Act, the program grew by leaps and bounds," said Umberto Saffiotti, M.D., currently chief of NCI's Laboratory of Experimental Pathology and in the 1970s, head of the carcinogen bioassay program.

Of the 252 hand-picked and highly suspect chemicals screened while the bioassay program was at NCI, 105 produced cancer in test animals. The bioassay program moved in 1978 to the National Institute of Environmental Health Sciences.

Naive Idea

"Some people had the straightforward, but naive, idea that we would simply find the carcinogens and that would save us all from cancer," Saffiotti said. "But bioassays alone would not solve the problem of cancer...bioassays have to be done along with mechanistic studies...side-by-side research..."

Rudimentary studies even in the 1940s had suggested that it took more than one action for a substance to cause cancer, but technology limitations slowed the work on developing this two-

hit theory. The theory hypothesized that exposure to an initiator might cause cancer, but exposure to an intitiator followed by a promoter would cause many more tumors.

Then in the 1970s, the late Elizabeth C. Miller, Ph.D., and her husband James A. Miller, Ph.D., of the University of Wisconsin McArdle Laboratory for Cancer Research in Madison, proved that many known carcinogens had to be converted to an active form in the body to initiate cancer—the first hit.

Dr. Elizabeth C. Miller and Dr. James A. Miller

In Search of

Carcinogens change from an inactive form to an active form via the enzyme system cytochrome P450. Converted to electrophiles, the activated carcinogens are in search of electrons from nucleophiles—and if the carcinogens end up taking electrons from the nucleophilic substance DNA, mutations (and thus initiation) result.

"There was a lot of confusion in the chemical carcinogenesis field because of the diversity of structures known to cause cancer," said Richard Adamson, Ph.D., director of NCI's Division of Cancer Etiology. "This confusion was resolved by the work of the Millers—it was a unifying theory about the way many different carcinogens worked."

In addition to clearing up confusion about how carcinogens caused the first hit, the discovery provided an explanation for observations that fruits and vegetables have a preventive effect for cancer. Carcinogens in search of electrons are oxidants and many substances in fruits and vegetables are natural antioxidants.

This discovery also led to a quicker way to initially screen carcinogens. Bruce N. Ames, Ph.D., at the University of California, Berkeley, used genetically developed bacteria to see if a chemical damaged DNA (mutation).

While not all chemical carcinogens are mutagenic in the Ames test, it is commonly one quick screening test used to initially evaluate a chemical's cancer-causing potential to man. "However, direct quantification of carcinogenicity from the Ames test is not appropriate," Adamson noted.

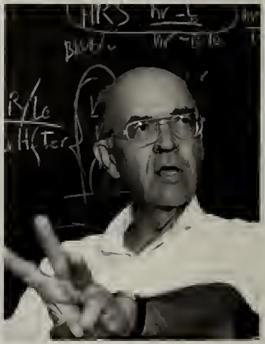
Promote or Prevent

Other cancer researchers refining and expanding on the two-hit theory looked at the next steps of carcinogenesis.

"We need ways to identify promoters because their elimination can have fast results," said former NCI director, Vincent T. DeVita, Jr., M.D., in 1981. As an example, both DeVita and Adamson have pointed out that the incidence of uterine cancers dropped drastically and rapidly in the mid-1970s when use of postmenopausal estrogens (a promoter for that cancer) was reduced.

Epidemiologists had also shown that while workers exposed to asbestos (an initiating substance) had more lung cancers, those exposed who also smoked cigarettes (which have multiple promoters) had rates more than 10 times higher.

Prevention via the promotion phase went further into the mechanisms of the cell. Roswell K. Boutwell, Ph.D., of the University of Wisconsin McArdle Laboratory, said his laboratory was researching the mechanisms of carcinogenesis "so that it could be described by molecular changes in the cells that are exposed to a promoting agent."



Dr. Roswell K. Boutwell

Mechanistic Approach

Boutwell and his colleagues then took a mechanistic approach to prevention, halting carcinogenesis in lab animals with a chemical. They found that certain tumor promoters increased the levels of various enzymes in the body. If the enzyme were blocked, the cancer could be prevented, they reasoned.

"The hypothesis was that if you prevented the molecular changes then you would prevent the appearance of a tumor," Boutwell explained. "And that proved to be true."

In the 1970s, in addition to knowing that fruits and vegetables had a valuable protective effect, studies of food intake were showing that high-fat, low-fiber diets seemed to increase the risk of some cancers. Many researchers and health professionals began to believe that an appropriate diet could combat cancer promotion.

Under congressional pressure in 1979, NCI issued "prudent, interim" dietary guidelines for cancer risk reduction. These guidelines recommended a reduction in total fat, an increase in dietary fiber, consumption of more fresh fruits and vegetables, avoidance of obesity, and moderation in alcohol use.

Worried about the evidence supporting those interim guidelines, NCI took the additional step of commissioning the National Academy of Sciences to review scientific data on diet and cancer. The NAS was to develop sound diet and cancer recommendations and a plan for further research on diet and cancer.

While the resulting 1982 report stated that details of the diet/cancer connection were not complete, the NAS said that the connection was clear enough for dietary recommendations for the public. In 1985, based on the NAS report, NCI issued its current guidelines.

More recent reviews of the expanded data on diet and cancer written by the Surgeon General in 1988 and the NAS in 1989 also support NCI's guidelines. The 1985 guidelines were reviewed in March 1990 and only modest updates in the wording were suggested.

"Chemo-Prevent"

As the mechanisms of carcinogenesis were being unraveled in the 1970s, researcher Michael Sporn, M.D., chief of NCI's Laboratory of Chemoprevention, was one of the researchers working to find ways to stop the process.

Sporn, who is often given credit for coining the term "chemoprevention" around 1977, used retinoids—a component of the fruits and vegetables thought to be protective—to halt carcinogenesis in animals.

Beginning in the early 1980s, beta-carotene, vitamins A, C, and D, fiber, calcium, and selenium have all been tried as preventive agents, first in animals and now in humans. The first randomized prevention trials are currently producing results, and more trials are under way.

Forthcoming Answers

Dr. Frank Meyskens, Jr.

"The results of large, definitive trials that were started in the mid- to late 1980s will be forthcoming and will answer some fairly major questions between now and the year 2000," said Frank Meyskens, Jr., M.D., director of the University of California-Irvine Clinical Cancer Center.

"And there is a whole slew of new cancer prevention agents that have been discovered in the last decade that are coming into the pipeline for human experimentation," he added.

Plants such as garlic, flaxseed, licorice root, citrus fruits, as well as drugs and other substances are under study in the hopes of finding substances that interrupt the carcinogenic process.

Herbert Pierson, Ph.D., a toxicologist in NCI's Division of Cancer Prevention and Control, used citrus fruits as an example. "The citrus as a whole fruit has practically every species of phytochemical that has been studied."

"They have carotenoids, flavonoids, terpenes, limonoids, coumarins—all of the classes of natural products that as individual pure materials neutralize the activity of powerful chemical carcinogens in animals," he explained.

Designer Foods

Pierson heads a project known as the Designer Food Program, which is researching the anti-cancer effects of food components. By also studying the human metabolism of these food components, he hopes the program scientists can elucidate how carcinogenesis is blocked.

Ultimately, the chemicals found to block cancer through this type of research could be put into food specifically to prevent tumors. Boutwell said, "If they can identify a compound and chemists can modify the structure and make it more active, we can do like we do with iodine and add it to salt, or like thiamine and add it to bread and doughnuts."

"Eventually that is the goal. . . find chemicals that are absolutely not toxic but will inhibit the development of cancer," Boutwell said. "That's the dream."

1971—1991: Diagnosis and Treatment Advances Improve Survival

By Hugh McIntosh

Advances in diagnosis and treatment over the past 20 years are adding years to the lives of people who get cancer, a fact illustrated by the tale of two athletes: Charlie Hickcox, a champion swimmer at the 1968 Olympics, and Brian Piccolo, then a star running back for the Chicago Bears football team.

Piccolo died in 1970 of testicular cancer, the No. 1 malignancy of men age 20 to 35. Ten years later, Hickcox got it too. But during that decade, the drug cisplatin (or platinum) was developed and incorporated into a treatment that quickly made testicular cancer one of the most curable of all malignancies.

"Brian Piccolo may well have been able to have been cured if he had the same diagnosis now," said Lawrence Einhorn, M.D., of Indiana University Hospital. "Charlie Hickcox was cured of his disease because he developed [it] . . . when platinum was around."

The impact of the new treatment stands out clearly in the data collected by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. They show an estimated 92% of patients diagnosed with testicular cancer between 1981 and 1986 were still alive 5 years later, compared with only 78% of those diagnosed between 1974 and 1976.

SEER Data

SEER also shows significant real survival improvement for Hodgkin's disease and childhood malignancies as well as smaller increases for most major cancers.

SEER was established following passage of the National Cancer Act of 1971. The program began collecting data in 1973 and now samples 9.6% of the U.S. population, covering five states and four metropolitan areas across the country.

It estimates rates for cancer survival, incidence, and mortality. Survival rates tell how long cancer patients live. If better diagnostics and treatments are developed, cancer patients live longer. Many, like Charlie Hickcox, are cured.

The SEER data point out two disparities in overall survival. Rates for blacks are about 14 percentage points lower than those for whites, and rates for people 65 and older are about 9 points lower than those for younger people.

The overall trend for blacks has shown no increase and now stands at 38.2% for patients diagnosed between 1981 and 1986, contrasted with a figure of 52.0% for white Americans.

Part of the reason for the lower figure is that the mix of cancers is somewhat different between blacks and whites, but there is no question that for some of the major cancers, such as breast, colorectal and uterine cancers, the survival rate among blacks is lower than among whites, according to Edward Sondik, Ph.D., deputy director of NCI's Division of Cancer Prevention and Control. Understanding and finding ways to alleviate these differences is a major challenge for the National Cancer Program, he said.

The disparity in survival figures between blacks and whites, said Harold Freeman, M.D., director of surgery at Harlem Hospital, is due primarily to economic status. But cultural differences also play a role.

Dr. Harold Freeman

"Poverty is the underlying factor," Freeman said. "We don't find any strong indication that race is related to cancer incidence or survival from a genetic point of view. [But] we do find that the cultural meaning of race is extraordinarily important."

Culture indicates lifestyle, values, traditions, diet, and other factors that influence cancer survival.

Why?

Poverty also plays a part in the poorer survival rates among older people, said Samuel Broder, M.D., director of NCI. So also do other illnesses, chronic diseases, lack of mobility, and the lack of awareness among physicians that cancers in older persons should be treated seriously.

"It's important to come to terms with the fact that we make sure there isn't an arbitrary cutoff, that people over 65 are important, productive members of society," Broder said. "We have to make sure that we're reaching them with the best prevention, diagnosis, and treatment."

Rising survival rates since 1971 reflect a shift of physicians and patients to a more aggressive, more optimistic approach to treatment, said Michael A. Friedman, M.D., associate director of NCI's Cancer Therapy Evaluation Program.

"This enthusiasm for treatment certainly is at the base of all the progress because if you don't have the sense that there are improvements to be made, then those improvements won't be looked for," he said.

Systemic Treatment

Because most cancers can only be cured by systemic treatment, many researchers have concentrated on chemotherapy over the past 20 years. New drugs, such as cisplatin and doxoru-bicin, plus new knowledge about drugs and cancer biology have allowed them to develop more effective treatments.

The rise in testicular cancer survival, for example, is largely due to cisplatin. The introduction in the 1970s of computerized axial tomography (CT) scanning also helped, allowing better diagnosis and then more specific therapy.

Testicular cancer is also remarkable for the speed with which the new therapy was disseminated, said Larry Kessler, Sc.D., chief of NCI's Applied Research Branch. Just 3 years after publication of the advance, national survival data were already beginning to show the impact of cisplatin.

Survival improvement in Hodgkin's disease and the overall increase in childhood cancer survival represent, in part, the fine tuning and dissemination of pre-1971 therapy breakthroughs. Much of the work took place in clinical trials sponsored by NCI.

"The main influence of the national trials has been the dissemination of knowledge and of technology," said Donald Pinkel, M.D., University of Texas M.D. Anderson Cancer Center.

5-Year Relative Survival Rates

Percent by selected sites
SEER Program
All races, males and females

Site	**Year of diagnosis 1974-76**	**1981-86**
All sites	49.0	50.7*
Oral cavity & pharynx	52.9	50.9
Esophagus	4.7	8.0*
Stomach	14.9	17.0*
Colon/rectum	49.3	55.5*
Liver	3.8	4.5*
Pancreas	2.7	3.1*
Larynx	65.3	67.0
Lung & bronchus	12.2	13.1*
Melanoma of skin	79.2	81.1*
Breast (females)	74.0	76.6*
Cervix uteri	68.3	65.8*
Corpus uteri	88.2	82.6*
Ovary	36.5	38.9*
Prostate gland	66.5	73.3*
Testis	78.4	92.1*
Urinary bladder	72.2	78.2*
Kidney & renal pelvis	51.4	52.6
Brain & nervous system	22.1	24.8*
Thyroid gland	91.8	94.2*
Hodgkin's disease	70.9	75.9*
Non-Hodgkin's disease	46.9	50.8*
Multiple myeloma	24.3	26.4*
Leukemia	33.4	34.9

*The difference in rates between 1974-76 and 1981-86 is statistically significant (P<.05)

Training

Another influence of national trials has been the "training of people to use protocols and not just fly by the seat of the pants when they treat youngsters with cancer," he added.

Survival rates for acute lymphocytic leukemia increased 19.4 percentage points to an estimated 72.8% in white children (numbers of cases for other children are small and not reported separately) diagnosed between 1981 and 1986 compared with those diagnosed between 1974 and 1976. Survival rates for non-Hodgkin's lymphoma rose 26 percentage points during that time to 68.3%. The data on bone cancer—which show a rise of only 1.9 percentage points to 53.8%—however, hide the most recent success in childhood malignancies: osteosarcoma.

In the 1960s, only 20% of white adolescents who got osteosarcoma survived, even after amputation of the diseased limb. But the introduction of doxorubicin in the early 1970s and other advances led to chemotherapies that more than tripled the cure rate.

"We know in our clinical trials that 60% to 70% of the people get on the disease-free survival curve and stay there for years," said Emil Frei, III, M.D., director of the Dana-Farber Cancer Institute, Boston. "We also found we could avoid amputation because of response to chemotherapy in some 60% or 70% of the patients."

Survival improvements in some of the leading cancer killers—lung, prostate, and breast—have been small to modest. Lung cancer has proved difficult to treat, so the strongest efforts to control it have gone toward prevention.

Early Diagnosis

In the other two cancers, early diagnosis seems to be responsible, in part, for improvements in the national (SEER) survival data.

Some experts question whether some improvements are real. Early diagnosis usually means that a cancer has been detected at an earlier, more curable stage. But if tumors discovered by early diagnosis are a type that would not lead to death, the survival rate goes up without a real increase in survival.

This may be happening in prostate cancer. "The reason survival is going up . . . is not due to a great advance in treatment," according to NCI's Sondik, "I believe it's primarily due to finding more of the latent disease."

Survival rates for colorectal cancer, another leading cancer killer, have risen markedly. The

increases could be due to any combination of early detection, treatment improvement, change in the disease, or statistical artifact.

Nevertheless, the recent development of chemotherapies with fluorouracil and levamisole foreshadows real progress. "We've got good, highly significant survival improvements in randomized studies," said Charles Moertel, M.D., of the Mayo Clinic, Rochester, Minn.

He expects the therapies "to have a major impact on the [national] colorectal death rate in the years immediately ahead."

SEER shows a modest survival increase in breast cancer, the most common major malignancy in the United States. Some experts credit improved chemotherapy; others point to more early detection through mammography.

Breast cancer "is starting to be detected earlier, and that should . . . eventually result in better survival rates," said Lawrence Garfinkel, statistical consultant to the American Cancer Society. "But you can't demonstrate [improved survival] on a national basis."

Bladder Improvements

Data show good survival improvement for urinary bladder cancer. Chemotherapy and radiotherapy may have contributed to the rise. Early diagnosis, as a side effect of the increased use of transurethral resection, may be involved.

The improvement may also result from the way this cancer is categorized, said Eli Glatstein, M.D., NCI's chief of radiation oncology. Some pathologists who classify bladder cancer include noninvasive carcinoma in situ, but others don't.

He cautioned against making survival comparisons with historical data. Staging now is better, patients are categorized differently, and CT scans pick up tumors that would have been missed 20 years ago.

Downward survival trends for oral, cervical, and uterine body cancer in the SEER data do not indicate lower probabilities of survival, but result instead from the mathematical computation of survival. For example, the change in oral cancer rates is not statistically significant.

Cervical Cancer

For cervical cancer, early detection through Pap smears is pushing the death rate down. But cervical cancer survival rates are calculated only for those cancers detected at the invasive stage. So as cancers are found at an early, noninvasive stage and cured, the survival rates are based on fewer invasive cancers that are detected at later stages. Therefore, the cancer survival rate decreases.

The downward trend in the survival figures for uterine body cancer also appears to mask the improvements in controlling the disease. Many prescriptions for exogenous estrogens for menopausal symptoms were written in the late 1960s and early 1970s. The estrogens generated tumors with very good prognosis, temporarily improving the survival rate for the entire group of uterine cases.

A Food and Drug Administration warning in 1976 caused a sharp drop in the use of exogenous estrogens and corresponding downturns in uterine cancer incidence and survival. But throughout the ups and downs of incidence and survival, the mortality rate has dropped steadily, Sondik said, "so there is no doubt that there is an improvement in controlling the disease."

The overall picture drawn by SEER data shows slow, steady improvement in the 5-year survival rates for cancer over the past two decades. But, the data also reveal where improvements need to be made.

"None of us can be happy with the 5-year survival figures as they exist," Broder said. "We would like to see the kind of progress we've made against Hodgkin's disease and testicular cancer applied across the board . . . . The good news and the bad news should serve as an impetus for us to redouble our efforts."

National Cancer Program Created Network for Delivering Research Results

By Patricia A. Newman and Michael E. Newman

Landmark legislation passed in 1971 enabled the National Cancer Institute to develop a national program with broad scientific and public impact.

In addition to expanding and intensifying cancer research, the National Cancer Act provided mandates and resources to allow NCI to create a meshwork of facilities, trained physicians and scientists, and information systems to deliver research findings to the public and health professionals.

New programs trained a cadre of experts in cancer treatment, expanded cancer centers, linked clinical research to community cancer care, and developed new and nontraditional approaches to information dissemination.

As a way of increasing the national capacity to deliver modern cancer treatment, the 1971 Act authorized clinical training programs for health professionals. This was a nontraditional activity for the National Institutes of Health: other institutes could train researchers, but not clinicians.

Medical oncology became a board-certified specialty in 1972. The number of certified medical oncologists rose from fewer than 100 then to nearly 5,000 in 1989. Pediatric hematology/oncology soon followed.

Champion

B.J. Kennedy, M.D., of the University of Minnesota Medical School, championed the development of medical oncology, and thinks that in the future, as the U.S. population ages, the need for medical oncologists will increase.

"They coordinate the care of older patients. I tell young medical students now to combine geriatrics with oncology," Kennedy said.

The number of radiation oncologists also has risen since the 1970s. Although surgeons do not have board certification in oncology, the Society for Surgical Oncology now requires new members to complete an approved training program in surgical oncology.

In the early 1980s NCI developed two key tools to speed research results to the clinic. One was PDQ (Physician Data Query); the other was the Community Clinical Oncology Program.

PDQ enables physicians to tap into, via a

library or their home or office computer, the latest information about cancer treatment and about ongoing clinical trials. It is still unique in the realm of medical databases.

"PDQ was the last piece of the package that we put together in terms of information transfer," remembered former NCI Director Vincent T. DeVita, Jr., M.D.

To move quickly to set up the database, DeVita sole-sourced a contract to the only company at the time with a software program that could handle the information flexibly. It was not easy because of bureaucratic impediments.

"We finally had a big meeting," said DeVita, "and a key individual in the approval process pulled out a book and said, 'you can't sole source it; there's no way you can do this unless it's a national emergency.'

"I said, 'the director of the NCI has the authority to declare a national emergency,' so I declared a national emergency. We sole-sourced the contract, and it took off."

CCOPs

NCI created the Community Clinical Oncology Program to involve a greater number of community physicians in clinical trials. The intent was to draw upon a greater patient pool for trials and to link together the community physician with investigators based either in academic institutions or cancer centers.

"Some of that kind of networking had been done in the Cooperative Group program, but we thought that if we could extend that by one more level to involve the community physicians, we'd enroll more patients in clinical trials and be able to get answers to clinical protocols faster," said former NCI Deputy Director Jane Henney, M.D., vice chancellor at the University of Kansas Medical Center.

Participating physicians would also find it easier to stay up to date with treatments evolving from research, she said.

Today, 51 NCI-funded CCOPs and 12 minority-based CCOPs are located in 32 states, the District of Columbia, and Puerto Rico. They involve 300 hospitals and 2,575 physicians. About 5,000 patients annually participate in clinical trials through the CCOP.

"People who were skeptical at one time in the past have now become firm believers," DeVita said.

Dr. John W. Yarbro

Cancer Centers

Perhaps most directly affected by the passage of the National Cancer Act were the nation's cancer centers.

"Prior to 1971, cancer centers were not well defined by NCI," said John W. Yarbro, M.D., Ph.D., professor of medicine at the University of Missouri School of Medicine and director of the NCI Centers Program from 1972 until 1975.

"The loose network then included three institutions that almost everyone regarded as comprehensive—M.D. Anderson in Houston, Roswell Park in Buffalo, and Memorial Sloan-Kettering in New York," said Yarbro.

The National Cancer Act expanded the mission of comprehensive cancer centers, calling for the establishment before 1974 of 15 new centers conducting clinical research, training, and demonstration of advanced diagnostic and treatment methods relating to cancer. By 1991, there were 24 comprehensive cancer centers in the nation.

Dr. William W. Shingleton

William W. Shingleton, M.D., founding director of Duke University's Comprehensive Cancer Center and a top adviser to NCI both before and after passage of the Act, said the Act's provision for comprehensive centers had a "crucial" impact on cancer treatment in the United States.

The centers, he said, recruited new investigators into cancer research, acquired private funds to supplement government spending, then developed multidisciplinary clinics that improved the care received by cancer patients.

The National Cancer Act also helped define the concept of "a specialized cancer center," said Yarbro. Today, there are 29 such institutions, designated as either "clinical" or "laboratory" cancer centers by NCI. The list includes such well-known research facilities as Cold Spring Harbor in New York, McArdle in Wisconsin, and St. Jude in Tennessee.

"The major difference between the cancer centers before and after 1971 was the emphasis on getting cancer control equitably distributed across the country," said Gerald P. Murphy, M.D., chief medical officer of the American Cancer Society, a former National Cancer Advisory Board member, and former director of the Roswell Park Memorial Cancer Center (now the Roswell Park Cancer Institute). Murphy said that before the National Cancer Act, cancer centers had no regional responsibilities for the populations they served. "Information dissemination, outreach programs, and community involvement weren't really addressed," he added.

Dr. Gerald P. Murphy

"I think the National Cancer Act emphasized networking by requiring the centers to engage in such activity and provide financial support to carry out the mission," said Murphy.

Place to Call

In 1973-1974, Elaine Freeman, then a public affairs officer at The Johns Hopkins Medical Institutions, spent 18 months on loan to NCI to figure out some way, through the comprehensive cancer centers, to give patients and family members access to the best available information about cancer.

Now, 17 years later, she feels those months produced one of the most satisfying achievements of her career—The Cancer Information Service. Freeman is director of public affairs at Hopkins.

In the early 1970s, she remembers, "some people, like Ted Kennedy's son, had access to the best advice, access to information that everybody ought to be able to get," said Freeman. "We decided to figure out some way, through the centers, of making that kind of information available to everyone."

Freeman visited the few comprehensive cancer centers, such as those at Roswell Park and the University of Wisconsin, that had some type of program already in place. "For most comprehensive centers, in those early years, communication was not the first priority," Freeman remembers.

Constrained

"We knew that the American Cancer Society had divisions in every state and units in a lot of cities, but no professionally trained people [to handle public calls]. Also, they were constrained in the information they were able to provide."

Convinced that a critical gap existed in the information patients could access easily, NCI created the Cancer Information Service by awarding sole-source contracts to comprehensive centers. Offices opened in 1976. The idea was to link the public directly to regional cancer centers supported by NCI.

CIS offices now are located at 22 institutions across the country and handle 550,000 calls annually. Although no longer limited to comprehensive centers, most CIS offices are located within such centers.

Marion Morra, who founded the Yale CIS in July 1976 and now is assistant director of the Yale Comprehensive Cancer Center, saw an enormous change in the resources available to her counselors in those early years.

"The only things we had then were one- or two-page pamphlets from ACS and a few publi-

cations from NCI. We spent a lot of time putting together information to answer the phones. Now we have volumes of patient education materials, computers, and PDQ," Morra said.

The other big change is that then "people did not know as much as they do now about cancer. Also, people found it difficult to talk about the disease. There were not as many stories in the news. It was just the beginning of people living longer with the disease." Today's callers, Morra said, ask more complex questions.

Eternal Vigilance

"By 1984, we had substantially fulfilled the mandate [of the Act] in terms of [establishing] an organizational network. From there, the problem is keeping it financed and retaining [NCI's] independent authorities," said DeVita. He added that the network "requires eternal vigilance to keep it going."

The network also must be flexible to meet changing needs. For example, in 1989, the National Black Leadership Initiative was established to organize community coalitions on cancer prevention for blacks.

DeVita said that the framers of the National Cancer Program, "like the framers of the Constitution, made [the Act] general enough so if you were willing to use it and take the heat, it works. . . . Now that it's all operationallly intact, if you infused a billion dollars into it on top of what you've already got, it would take off like a big bird."

Twenty Years of Progress in Immunology Research Is Ready for Harvest

By Elaine Blume

Cancer treatment entered the gene therapy age on January 29, 1991, when two melanoma patients were infused with their own genetically altered cells. The occasion marked the culmination of two decades of dramatic advances in molecular genetics.

But immunologists, too, had reason to celebrate. The cells used in the treatment were tumor-infiltrating lymphocytes. Their growth in the laboratory was made possible by the immune system component interleukin-2. It was expected that the infused cells would launch an immunologic attack on the patients' cancers.

And the researchers hoped the cells would strike with added force because they had been engineered to carry an extra copy of the tumor necrosis factor gene—a gene whose cancer-fighting product is also part of the immune system.

"We need to improve TIL therapy, and one way may be with the addition of genes that can stimulate the production of anti-tumor toxins," said Steven A. Rosenberg, M.D., Ph.D., chief of the National Cancer Institute's Surgery Branch.

Immunology and Cancer

Gene therapy is not the only cancer breakthrough that owes a major debt to progress in immunology. Labeled monoclonal antibodies are now being employed experimentally to visualize the spread of tumors and monitor their response to treatment. In addition, monoclonals conjugated to radioactive isotopes or toxins are being used in treatment trials.

Bone marrow transplants are another immunologic advance that is changing cancer therapy. "Use of autologous marrow transplants allows for more intense and thus more effective treatment," noted Faye Austin, Ph.D., chief of NCI's Cancer Immunology Branch.

Marrow Transplants

Doctors using autologous marrow transplants remove some of the patient's bone marrow prior to chemotherapy. After administration of drug doses so high that they destroy the patient's immune system, the stored marrow is returned to the patient to reconstitute that system.

In a move that stimulated much interest, Blue Cross and Blue Shield recently announced that some of its local plans would cooperate with the government to finance trials of autologous bone marrow transplants in the treatment of metastatic breast cancer.

The National Cancer Act cannot claim sole responsibility for the impressive accomplish-

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ments of immunology during the last 20 years. But it would be difficult to argue that the field would have moved so far so fast in the absence of the Act.

The development of genetic engineering in the early 1970s effected a biomedical revolution. This revolution profoundly altered research in immunology, even as immunology transformed genetics. By 1980, immunology was a molecular science, and it had contributed invaluable tools to biomedicine.

"Hybridoma technology and monoclonal antibodies had not been discovered at the time the Cancer Act came into being," said Thomas Waldmann, M.D., chief of NCI's Metabolism Branch. "Their development was an outgrowth of Mike Potter's work with myeloma protein-producing cells." (Potter, a physician-scientist, is the chief of NCI's Laboratory of Genetics.)

Monoclonal Antibodies

Early efforts to use monoclonal antibodies in cancer therapy were largely unsuccessful, according to Waldmann, but he believes their current prospects are encouraging.

"We now know enough about growth factors, such as lymphokines, to be able to direct antibodies against key growth factor receptors," he explained.

Waldmann and his colleagues have been studying the use of monoclonal antibodies directed toward IL-2 receptors as a potential cancer treatment. This approach has the advantage that, although these receptors are expressed on certain cancer cells, they are not present on normal resting cells.

"We are also becoming able to 'humanize' mouse monoclonals with genetic engineering," Waldmann said, "and eventually, human monoclonals will be available." Unlike murine antibodies, humanized and human monoclonals are not destroyed by the patient's immune response.

Waldmann also explained that humanized, but not murine, antibodies are able to harness the patient's cellular immunity against the target. "I expect scores of humanized monoclonals to become available within the next few years," he said.

"And finally," he added, "we are learning how to arm monoclonals with radioactive isotopes or toxins. This should add significantly to their effectiveness, especially in a disease like cancer, where it is essential that you kill every malignant cell."

Monoclonal antibodies are just one of the critical tools that immunology has given medical research in recent years.

Immunodeficient "nude" mice have become mainstays of chemotherapy screens because they will accept transplanted human tumors. More recently, SCID-hu mice, which possess the equivalent of a human immune system, have taken their place in the ranks of major test systems for AIDS, cancer, and other vaccines.

Other techniques immunology has provided—Western blots for separating and identifying cellular proteins and ELISA tests for detecting minute amounts of antigens—have

Dr. Sheldon Cohen

proven indispensable to basic investigations in every area of medical science.

But perhaps the most notable change in immunology during the past 20 years has been scientists' altered view of the immune system.

"We have come to look at the immune system as a community of one trillion leukocytes—an interlocking group of lymphoid organs in which trafficking of cells occurs," said Sheldon Cohen, M.D., scientific adviser to the director of the National Institute of Allergy and Infectious Diseases.

Communication

"We have learned a great deal about the way in which the elements of this system—the leukocytes—communicate via secretions, and the effect of these secretions on other cells. We have also learned much more in recent years about the interrelations between the immune, neural, and endocrine systems," he added.

The secretions Cohen is referring to are the cytokines. Sometimes called "hormones of the immune system," they encompass the monokines, produced by monocytes and macrophages, and lymphokines, secreted by lymphocytes.

IL-2, the substance used to grow lymphocytes in cell culture for use in gene therapy, is one of the lymphokines. In the body, it plays a key role in regulating the immune response.

The immune system may be regulated in another way as well.

Idiotypes—the variable regions of antibodies that recognize specific antigens—are themselves collections of antigenic determinants that can induce complementary antibodies, known as anti-idiotypes. Anti-idiotypes, in turn, may give rise to anti-anti-idiotypes, and so on, in an expanding network that, one theory holds, may switch on, enhance, or shut off the immune response.

Fundamental Facts

Increased understanding of the immune system has directly influenced cancer research.

"In the early 1970s, we didn't understand why there was an MHC (major histocompatibility complex)," said David H. Sachs, M.D., chief of NCI's Immunology Branch. "We knew there was such a complex because it caused rejection of transplants, but that clearly wasn't why it was there. Now we know that it is there to present foreign antigens to the immune system, and that it is involved in many immune responses, including responses to cancer."

Immunologists have learned that two classes of surface molecules on T lymphocytes, both controlled by MHC genes, mediate the interaction between T cells and their targets. These surface molecules bind to antigens and present them to specific receptors on other T cells.

Researchers have identified and studied specific antigenic sites recognized by T cells, and have found that these cells can recognize sites belonging to intracellular as well as surface proteins. This discovery suggests that the abnormal proteins produced by oncogene mutations are potential immune targets—and potential material for anti-cancer vaccines.

Patients and doctors might look askance at the idea of injecting oncogene products into humans in order to induce immunity. But researchers see a possible way around this difficulty.

Anti-idiotype antibodies can serve as stand-ins for antigens, potentially inducing immune responses that will destroy the original antigens. Thus an antigen that cannot be easily purified or that poses safety hazards could still form the basis of a vaccine.

"The major progress in our basic understanding of the immune system has finally enabled us to move toward the rational design of vaccines for diseases like cancer and AIDS, where conventional approaches may not be successful," said Jay Berzofsky, M.D., Ph.D.

Berzofsky heads NCI's Molecular Immunogenetics and Vaccine Research Section, which has played a leading role in describing how T cells recognize and respond to antigens.

Outlook

Immunology has developed in parallel with molecular genetics, and the two sciences have arrived at roughly the same place.

In both disciplines, advances in basic knowledge during the past 20 years have resulted in a bevy of Nobel prizes. In both disciplines, too, while progress in theoretical knowledge has contributed to some clinical advances, the big payoffs lie ahead. In immunology, these include the ability to induce tolerance of organ transplants and the development of safe and effective cancer vaccines.

Cancer researchers and immunologists are sanguine.

"We have seen the long gestation period of 20 years to develop insights that now can bear fruit in terms of prevention and treatment," said NCI's Waldmann. "It is to be expected that it takes a while to exploit these new insights. I think we have, in basic science, planted the fruit tree. Now we are ready for the harvest."

Twenty Years Mark Success Against Tobacco Use

By Cori Vanchieri and Jill Waalen

In the early 1970s, office buildings of the National Institutes of Health had cigarette machines on each floor, college parties were called "smokers," and nonsmokers could only choose from the first few rows on commercial airplanes to avoid cigarette smoke.

Today, people who smoke at work are forced to huddle outdoors, a state supreme court judge has ordered a mother to stop smoking in front of her child, and virtually all domestic flights are smoke free.

This turnaround is due to a shift in the public's attitude toward smoking, new policies restricting tobacco access, and the Surgeon General's ongoing compilation of evidence on the dangers of tobacco use, according to Donald R. Shopland, coordinator of the National Cancer Institute's Smoking and Tobacco Control Program.

Emmanuel Farber, M.D., Ph.D., a member of the first Surgeon General's Advisory Committee on Smoking and Health in 1964, is amazed by the pace of the progress of the past 20 years. "We [the committee] didn't think we'd see any progress in our lifetimes," he said. "Now the smoking situation has turned around 180 degrees."

Consumption Drop

Per capita cigarette consumption in 1989 dropped below 3,000 cigarettes, a significant decrease from a 1970s high of more than 4,000 (see figure 1). Smoking prevalence began its decline after release of the 1964 report, which concluded that "cigarette smoking is a cause of lung cancer in men and a suspected cause of lung cancer in women."

But prevalence did not begin a serious downturn until 1976. In 1970, prevalence was 37%, in 1976 it was 36%, and by 1987 it had dropped to 29% of U.S. adults aged 20 and older (see figure 2).

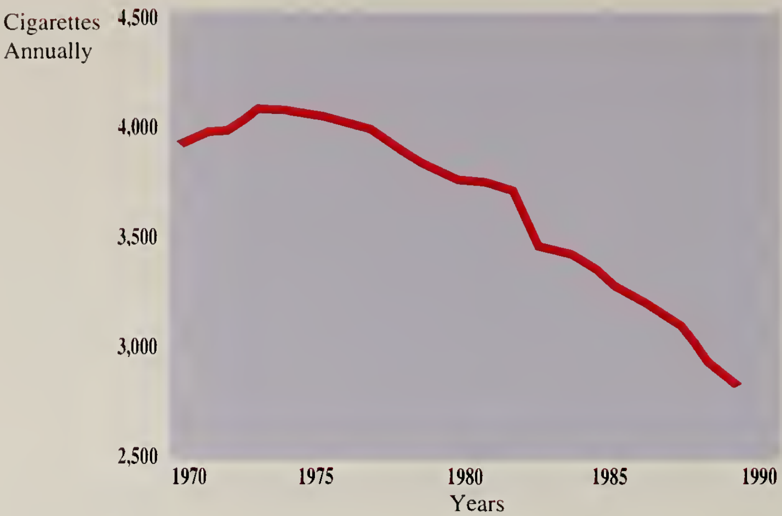
Farber, now at the University of Toronto, credits the 1971 National Cancer Act with giving anti-smoking efforts a push.

"The emphasis on cancer created by Nixon's War on Cancer helped because it made people aware that they could do something about cancer—that you can avoid things, like smoking, that can cause it," he said.

Although no special emphasis was placed on smoking in the National Cancer Act, some of the extra funds provided to NCI by the Act fueled smoking research activities.

In 1971, NCI's Smoking, Tobacco, and Cancer Program was trying to identify less haz-

Figure 1—U.S. Per Capita Cigarette Consumption 1970—1990



Perhaps the most influential Surgeon General's report since 1964 came in 1986 with the conclusion that "involuntary smoking is a cause of disease, including lung cancer, in healthy nonsmokers."

Policy Push

"A lot of states have used the 1986 Surgeon General's report as background for changing public policy to protect people from environmental tobacco smoke," said Rose Mary Romano of the Centers for Disease Control Office on Smoking and Health.

ardous cigarettes, said Gio B. Gori, Ph.D., then deputy director of NCI's Division of Cancer Cause and Prevention (now the Division of Cancer Etiology).

"The original program recognized that people would smoke despite all the warnings," he said.

In the 1960s, the average tar content was about 50 mg per cigarette. By the end of the 1970s, it was below 20 mg, according to Gori. Nicotine levels were also reduced.

By the early 1980s, hopes for a less hazardous cigarette had fizzled. The 1981 Surgeon General's report showed that while use of these cigarettes appeared to decrease the risk of lung cancer somewhat, it did nothing to avert cardiovascular damage or other health risks. The only option for smokers was to quit.

Smoking Indicted

The stream of Surgeon General's reports since 1964 have indicted cigarette smoking not only as contributing to cancers of the lung, mouth, esophagus, bladder, pancreas, kidney, and cervix, but as a far-ranging health hazard, linked to heart disease, stroke, emphysema, immunosuppression, and allergies. In women smokers, oral contraceptives potentiate the harmful effects of smoking on the cardiovascular system.

Policy changes have been swift, with state laws to restrict smoking in public places multiplying in the mid 1970s, and numbering 43 states today.

These laws range from the simple, such as no smoking on a school bus while the bus is in operation (South Carolina) to comprehensive clean indoor air laws that limit or ban smoking in virtually all public places. Minnesota's extensive law includes restaurants and private workplaces.

More than 440 cities and counties have passed ordinances even more restrictive than their statewide counterparts.

All 50 states and the District of Columbia have placed excise taxes on cigarettes, ranging from $.40 per pack in Connecticut to $.02 per pack in North Carolina. In 1989, nine states increased their cigarette excise taxes; California's jumped from $.10 to $.35.

These tariffs seem to help. Just a 10% price increase has been shown to produce a 4%—5% consumption decrease in adult smokers, with a 14% decrease among teenage smokers (see News, *J Natl Cancer Inst*, May 22, 1989).

Airline Ban

The airline ban, first limited in 1987 to domestic flights of 2 hours or less, was upgraded in 1990

Mark Pertschuk

to ban smoking on all domestic flights except about two dozen originating in Alaska and Hawaii.

This so called "epidemic of nonsmokers" and policy expansion is due to the "nonsmokers' rights movement," according to some of the movement's most vocal advocates.

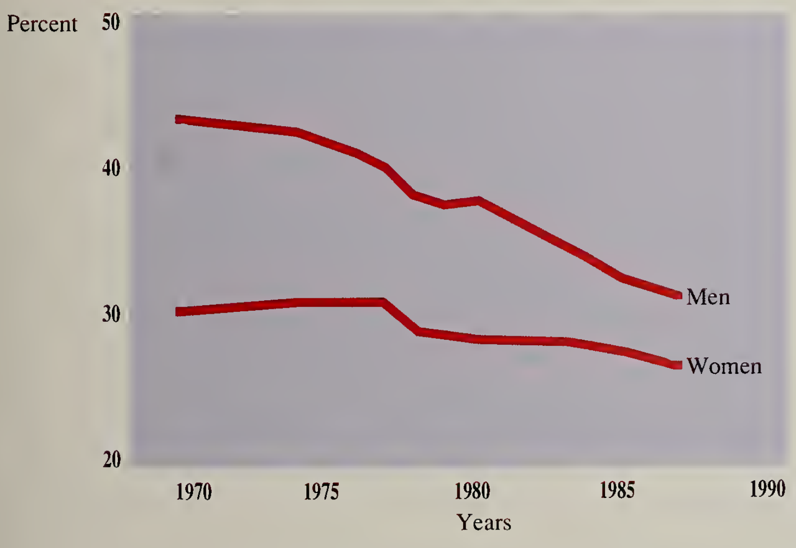
"There was a small handful of people pushing for nonsmokers' rights in the 1960s," according to Mark Pertschuk, executive director of Americans for Nonsmokers' Rights, Berkeley, Calif.

"Today there are lots of troops and leaders in the movement. For example, each of California's 60 local health departments has from 1 to 20 staff members devoted to tobacco," he said.

Add to each state's ranks the 60 or so local nonsmokers' rights organizations, the voluntary health agencies, and the private medical organizations.

The nonsmokers' rights movement grew rapidly when smoking came to be viewed as a health issue that affects nonsmokers, said Phil Wilbur, of the Washington, D.C.-based Advocacy Institute. With this change, all of the policy moves to protect nonsmokers made sense, he said.

Figure 2—Trends in Smoking Prevalence in U.S. Adults 1970—1987



Attitude Change

This change in public attitude was seen in a 1978 Roper Organization poll commissioned by the Tobacco Institute, which noted a sharp rise (from 46% to 58%) in the percentage of respondents who believed that passive smoking is harmful. The survey also found that the tobacco industry was considered less favorable by those surveyed than at any other time since 1968.

One result of this movement is the more than 60 lawsuits that have been brought against cigarette manufacturers, since 1980, naming them liable for smoking-related deaths.

Certain changes need to occur for this country to meet the Surgeon General's goal of a smoke-free society by the year 2000, according to experts.

"Once smoking is prohibited in all enclosed places to protect nonsmokers, and once advertising and promotion of cigarettes and tobacco products is eliminated, we will have essentially achieved our goals," said advocate Pertschuk.

The push for bans in public places will get a boost if the Environmental Protection Agency decides to label environmental tobacco smoke as a Class A carcinogen. A scientific advisory board to the EPA concluded that the classification should happen. EPA expects to make its decision this summer.

Although EPA has no regulatory authority over indoor air issues, its decision will carry a lot of weight in voluntary workplace decisions, according to the Advocacy Institute's Wilbur. It could also affect actions of the Occupational Safety and Health Administration, which has regulatory authority.

"Preemption Clause"

To restrict advertising, federal regulations are the most likely solution, Pertschuk said. The other way to go is to remove the "preemption clause" of the federal cigarette labeling act. The clause, requested by the tobacco industry, takes away the power of the states and local governments to regulate tobacco advertising.

With removal of this clause, "there would be a firestorm of activity" at the local level to ban billboards, Pertschuk added.

That would then leave magazine advertising. About 50 magazines, including *Good Housekeeping, National Geographic,* and *Modern Maturity* have voluntarily restricted tobacco advertising on their pages.

Even if advertising bans occur and indoor smoking policies are strengthened, special efforts will be needed to help smokers quit what Surgeon General C. Everett Koop, M.D., labeled an addictive habit.

Large-scale community studies are focusing on this area. The Community Intervention Trial (COMMIT) for Smoking Cessation is NCI's 10-community intervention study to test smoking cessation strategies, mainly for heavy smokers.

COMMIT is a prelude to the more extensive American Stop-Smoking Intervention Study (ASSIST), a joint NCI-American Cancer Society 20-community project, for which planning begins this year (see News, *J Natl Cancer Inst,* Feb. 6, 1991).

"As smoking becomes less socially acceptable, we must provide incentives and programs" to help smokers quit, Pertschuk said. "Both COMMIT and ASSIST can provide us with the knowledge of what works in the community in education, cessation, and prevention." These programs will have to outdo the tobacco industry's promotion efforts.

The Birmingham (Ala.) News recently told the story of a physician who was making a special effort to reach men with anti-smoking messages where they spend their time, in this case, at a local barbershop. While speaking to the men about the dangers of smoking, the physician was interrupted by two young women in short skirts who entered the shop and handed out free cigarette samples. He quickly lost his audience.

1971-1991: Biological Therapy Moves From Bench to Bedside

By Florence S. Antoine

For more than a century, scientists have been searching for ways to trigger the body's own defenses against cancer. During the past 20 years, progress in biological therapy has accelerated, uncovering a multitude of substances that boost, direct, or restore many of the normal defenses of the body.

Called biological response modifiers, or BRMs, many of these agents occur naturally in the body, while others can be made in the laboratory.

The studies of the past 20 years have led researchers to believe that biological agents may prove to be most beneficial when used in combination with other treatment modalities such as radiation and chemotherapy.

New Paradigm

After discovering the T-cell growth factor, interleukin-2, in 1976, National Cancer Institute scientist Robert C. Gallo, M.D., suggested that the time was ripe for developing new ways to clinically evaluate biologicals such as IL-2.

In 1978, the first human testing of a biological was under way. Clinical trials of alpha interferon, isolated in 1956 by virologists Alick Isaacs and Jean Lindenmann, began as a result of an American Cancer Society $2-million grant—then the largest research award in the organization's history.

In 1979, NCI announced it would buy $9 million worth of interferon for further human studies, and the ACS added another $3.8 million.

Most of the world's supply of alpha interferon was coming from Finland where virologist Kari Juhani Cantell, M.D., had developed a tedious, expensive, time-consuming extraction method requiring huge numbers of human leukocytes.

Limited Supply

Clinical testing of interferon was limited by its scarce supply and the impurities, or contaminants, often included in the natural preparation that was extracted from human leukocytes.

The interferon made up only about 1% of the entire mixture, making it difficult to distinguish between interferon's actions and those due to contaminants in the therapeutic mixture.

"Then, in 1981, recombinant DNA technology made possible the production of large quantities of pure alpha interferon at a reasonable cost," according to Vincent T. DeVita, Jr., M.D., then director of NCI, and now at Memorial Sloan-Kettering Cancer, New York.

Although alpha interferon did not turn out to be a magic bullet against cancer, it was found to be particularly effective against hairy cell leukemia, for which it received Food and Drug Administration approval in 1986.

Alpha interferon also seems to be useful against other cancers including low-grade lym-

phoma, chronic myelogenous leukemia, kidney cancer, melanoma, and multiple myeloma.

In 1988, it was licensed for two additional treatments—Kaposi's sarcoma and genital warts. This year it was approved for use against hepatitis C.

Filled Expectations

"Interferons have fulfilled all my expectations for anti-cancer therapy. Used alone, they can produce tumor shrinkage in 20% of patients with about a dozen kinds of cancers," said Ernest Borden, M.D., director of the Cancer Center of the Medical College of Wisconsin in Milwaukee.

Dr. Ernest Borden

He and other scientists are hopeful that the agent will produce promising results as a partner in treatment with other biologicals and/or treatment modalities.

In the 1980s, a cascade of other potential anti-cancer agents became available for human testing thanks to recombinant DNA technology. These substances included IL-2, tumor necrosis factor, and colony-stimulating factors.

"Ironically, it was IL-2, rather than interferon, that led scientists to validate the hypothesis that stimulation of the human immune system can lead to regression of certain cancers," Borden said.

Interferon, originally thought to control cancer growth through immune system modulation, turned out to play many roles, including that of direct inhibition of tumor cell growth. IL-2's role, primarily anti-tumor activity induced through a wide range of effects on the immune system, was more clearly defined.

Another biological approach, monoclonal antibody technology, underwent rapid development in the 1980s. But results of early clinical trials with mouse monoclonal antibodies as single-agent therapy against solid tumors were disappointing. In addition, patients developed immune responses against the mouse antibodies, precluding their repeated use.

Chimeras

Rather than abandon this approach, scientists are using recombinant DNA technology to develop chimeric antibodies with both human and mouse components.

A monoclonal antibody modification that has shown significant anti-cancer activity in patients binds antibodies with toxins or radioisotopes that can destroy cancer cells.

Dr. Ronald Levy

A more specific approach to monoclonal antibody therapy, first reported in 1982 by Ronald Levy, M.D., and co-workers at Stanford University, uses a custom-designed antibody to target the idiotype, a distinctive surface marker, on a patient's cancer cells.

Four patients with B-cell lymphomas who have received this therapy are in complete remission, 4 to almost 10 years after treatment.

"A drawback of this approach is that too often the patient dies before the custom-tailored monoclonal is generated," said Enrico Mihich, M.D., of Roswell Park Memorial Institute, Buffalo, N.Y., who led a 1978 NCI advisory subcommittee that recommended establishment of NCI's Biological Response Modifiers Program.

Dr. Enrico Mihich

Accelerate Production

To solve this problem, Levy's team has been working this past year to accelerate monoclonal antibody production by generating some that

may be cross-reactive among patients.

A monoclonal antibody treatment that could potentially save 30,000 to 100,000 lives each year was reported recently. Investigators in a large multicenter trial of more than 500 patients showed that the agent was safe and effective therapy for gram-negative bacteremia, a condition affecting many patients with diabetes mellitus, certain cancers, and burns.

Many investigators in the field of biological therapies predict more rapid progress in the 1990s, as scientists combine biologicals with each other and with other treatment modalities.

As the field matures, investigators are finding new and different uses for agents they had discovered earlier but had temporarily "shelved" because of ineffectiveness in earlier research applications.

For example, scientists reported last year that levamisole, used for more than 20 years as an intestinal deworming agent, significantly enhanced the biological activity of the chemotherapeutic drug 5-FU when the two agents were combined to treat Dukes' C colon cancer patients following surgery.

BCG Approved

The FDA approved last year live, weakened bacillus Calmette-Guérin, or BCG, for treatment of in situ bladder carcinoma. The anti-cancer potential of BCG, an attenuated form of the organism responsible for tuberculosis, had been investigated more than 30 years ago by Lloyd J. Old, M.D., of Memorial Sloan-Kettering, New York, and Baruj Benacerraf, M.D., then at the New York University Medical Center.

Old's studies of BCG led him, some 15 years later, to the discovery of tumor necrosis factor, or TNF, an anti-tumor factor produced in large amounts by mice after injection with BCG. TNF was put to new use in 1991, when the first cancer patients were treated with human gene therapy. A National Institutes of Health team, led by Steven A. Rosenberg, M.D., Ph.D., transfused two patients with recombinant TNF genes that had been inserted into TIL, special immune system cells capable of delivering the genes to the patient's tumor deposits where they could signal release of TNF.

In March, the FDA approved two types of colony-stimulating factors that can promote the growth of infection-fighting white blood cells in patients whose bone marrow becomes depleted during cancer therapy. G-CSF can potentially help 225,000 patients who annually receive high-dose chemotherapy or radiation therapy, and GM-CSF can help more than 3,000 patients who each year undergo bone marrow transplantations to treat their cancers.

"The licensing of these colony-stimulating factors is only the beginning. Chimeric hematopoietic growth factors that combine the activities of several growth factors, such as IL-3 and GM-CSF, in one molecular complex may soon be ready for clinical trials," said David Parkinson, M.D., of NCI's Cancer Therapy Evaluation Program.

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Oncology Professions Transformed in 20 Years: Patients Benefit

By Elaine Blume

When nurses graduating in the 1950s were asked in what fields they would like to practice, they placed oncology at the bottom of the list.

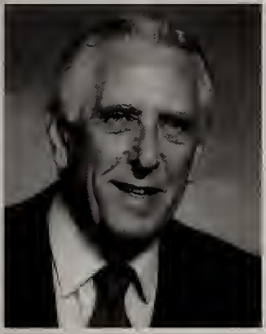
Young physicians found the field equally unattractive.

"I was told by many of my colleagues that I was out of my mind to go into the cancer world," said Arthur Holleb, M.D., a surgeon who was senior vice president for medical affairs and chief medical officer of the American Cancer Society from 1968 to 1988.

Training

Aided by passage of the National Cancer Act in 1971, times have definitely changed.

"A major benefit of the Act was the cancer education grants, which supplied fellowship money for the oncology training program," said B.J. Kennedy, M.D., of the University of Minnesota Medical School. "Those grants reached a high at one point of about $11 million annually."



Dr. B. J. Kennedy

The National Cancer Act was unique in authorizing support of clinical training programs. Because of the Act, NCI alone among components of the National Institutes of Health could support training of clinicians as well as researchers.

"The Act helped set up the national cancer centers and the whole program of cancer control," Holleb noted. "The comprehensive cancer centers were able to provide the specialized training for medical oncologists that changed the whole picture for Hodgkin's disease, leukemia in children, testicular cancer, and a whole bunch of different diseases that are now highly curable and which were uniformly fatal when I was a young resident."

Specialization

"Oncology is now very trendy," added Susan Baird, director of nursing at Fox Chase Cancer Center in Philadelphia, and editor of *Oncology Nursing Forum.*

"There's more to do because the focus of cancer care has changed," she noted. "In the 1940s and 1950s, cancer nursing dealt mostly with care of surgery patients and with death and dying. Now, nurses administer chemotherapy, manage its side effects, and are very involved in the psychosocial domain. And once nurses had more to do, oncology became more attractive to them."

As diagnostic and treatment modalities developed in the 1970s, specialization moved to the fore. And this change, say cancer practitioners, transformed their professions.

Certification in 1972

The American Board of Internal Medicine began in 1972 to offer certification in medical

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oncology. Minnesota's Kennedy was a leading figure in the movement to develop this subspecialty.

"There was obviously a need in internal medicine for people to take care of cancer patients, other than being asked whether the patient was a suitable candidate for surgical anesthesia," Kennedy said. "And with the development of chemotherapy agents, it increasingly became obvious that there was a very important role for the internist who was trained in taking care of and understanding the problems of cancer."

Dr. Arthur Holleb

Radiation therapy, according to Holleb, was at first just a moonlighting job for diagnostic radiologists, and was performed with low-voltage equipment. Later, radiation therapy evolved as an independent subspecialty of radiology, finally taking the name radiation oncology.

Ironically, surgery, the original locus of oncology, is the only major specialty that still lacks subspecialty certification in this discipline. In 1975, however, the Society for Surgical Oncology was formed from an earlier, less formal group. The organization now comprises 900 board-certified surgeons granted membership after passing a review.

Susan Baird

Key Players

Oncology nursing developed along with medical oncology, and cancer nurses soon found that they were crucial players in the oncology setting.

"A tremendous amount of nursing care in cancer is symptom management," said Fox Chase's Baird, "and that's what nurses are really good at. Because the problems keep changing along the course of the patient's disease, nurses have a real chance in cancer care to see what they can do."

Social workers also play key roles on oncology teams. "They counsel patients and families, lead support groups, put together home care plans, and identify available resources," said Arlene Robinovitch, director of services and rehabilitation at ACS.

Grouping Together

Professional organizations developed in tandem with specialization. The American Society of Clinical Oncology was founded in 1964 but grew slowly until the mid 1970s, when its membership reached 800. The organization then mushroomed to the 8,000 members it has at present.

"ASCO would not have grown as it did if it were not for the National Cancer Act," said Harvey H. Golomb, M.D., president of ASCO.

Pearl Moore

Pearl Moore, executive director of the Oncology Nursing Society, also credits the Act with fostering the growth of both the subspecialty of cancer nursing and of the ONS, which now has more than 17,000 members. "In 1971 there were a few of us out there," she said, "but we didn't label cancer nursing as a subspecialty, really. We were sort of all on our own, trying to find our way. The beginning of ONS paralleled the beginning of the specialty. And I think the National Cancer Act had a big part to play in this."

Nursing Research

Like Holleb, Moore regards the development of comprehensive cancer centers as a key achieve-

ment of the Act. She believes the centers were a major stimulus for specialization and for the growth of ONS.

She recalls that in 1972 she received one of the first master's degrees in cancer nursing. "For a long time, there were just five programs granting such degrees," she said. "Now there are about 40."

The Act also supplied funds for nursing research.

Patricia Greene

"What we did and the way we cared for patients was traditional," said Patricia Greene, ACS vice president for nursing, "but there wasn't a lot of research to support the appropriateness of one nursing intervention versus another. Just as with other areas of nursing research, cancer nursing research has developed and given us a sounder foundation for our practice."

Growth of clinical trials under the National Cancer Act also greatly affected oncology.

"The willingness of patients to participate in clinical trials and the willingness of physicians to enter patients into clinical trials have given us a whole new approach to the treatment of cancer," Holleb said. "In the past you used to take credit for how much you could do to the patient, and now it's how little you can do to the patient and get the same result."

Holleb also noted that cancer care has improved at the community level, where most patients receive their treatment. He points to the fact that many board-certified oncology subspecialists now work in community hospitals.

"With these factors, plus the increase in the number of good cancer control programs, plus the development of comprehensive cancer centers and specialty centers," he concluded, "care of the cancer patient is far better today than it was at the time the National Cancer Act began."

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1971-1991: Clinical Trials Evolve To Become Rigorous Scientific Testing Ground

By Hugh McIntosh

Since passage of the 1971 National Cancer Act, clinical trials have developed into mature research tools with the power to evaluate treatments for rare and common cancers alike.

They promise even greater advances in the future, not only for treating cancer, but for preventing it. However, the last two decades have also shown that clinical trials have limitations in the realm of cancer detection.

Clinical trials have been notably successful in developing treatments, particularly adjuvant chemotherapy, against solid tumors. "Prior to 1971, I think we were convinced we could cure hematological malignancies, but some of the more common tumors weren't amenable to treatment," said Bruce Chabner, M.D., director of the National Cancer Institute's Division of Cancer Treatment.

Success

Since 1971, clinical studies on cancer of the breast, colon, and rectum have shown that some common cancers can be treated successfully. By 1988, in fact, trials showing an effective treatment for early breast cancer prompted NCI to issue a "clinical alert" to inform physicians of the results before journal publication. This announcement on breast cancer was followed by clinical announcements to physicians on colon cancer in 1989 and rectal cancer in 1991.

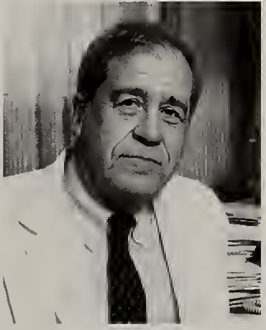
Effective therapies also emerged from clinical trials on less-common cancers, including testicular cancer, osteosarcoma, and a host of childhood malignancies.

"What we now know about how to cure cancers of children, [a cure rate] which is probably up to around 60% . . . has been learned from clinical trials," said G. Denman Hammond, M.D., chairman of the Children's Cancer Study Group.

First Trials

The first modern clinical trial of any type was reportedly a tuberculosis study performed by the British in 1948. Cancer clinical trials in the United States began in the mid-1950s.

In its simplest form, a clinical trial tests a treatment or other intervention in a group of patients. But the random assignment of some patients to a treatment group and others to a control group has gradually become the accepted practice for the large phase III trials that compare new interventions to standard ones.


Dr. Bernard Fisher

Over the past two decades clinical trials have evolved from the Dark Ages of witchcraft, in the words of one investigator, into a rig-

orous scientific discipline with a high degree of credibility among scientists and the public.

"Clinical trials are an extension of the scientific method," said Bernard Fisher, M.D., director of the National Surgical Adjuvant Breast and Bowel Project, one of the NCI-supported groups conducting clinical trials. "To a great extent, what we're testing are biological principles."

Innovations

Advances in biological science have enabled clinical trials to answer more innovative questions than before. New understanding about the heterogeneity of tumors and patients allows investigators to better assess a patient's response to therapies and to tailor treatments for the best results.

In addition, investigators are asking more biological questions during trials, looking for biological signs and markers to help predict patient response.

Consequently, laboratory scientists—experts in cytogenetics, immunology, molecular biology, and other specialties—are now essential to clinical research teams for the sophisticated laboratory tests used in determining tumor stage, diagnosis, and treatment. In the Children's Cancer Study Group, for example, about 14% of members are basic scientists.

Statisticians

The complexity of modern clinical trials, the demand for scientific rigor, and the need to demonstrate the reality of the incremental advances being made in cancer treatment have elevated the role of statisticians. Also, advances in statistical methodology, as well as in computers and computer programs, have given statisticians more to offer and raised their credibility.

The demands of clinical trials prompted cancer statisticians to develop new methodologies, said Richard Simon, Ph.D., chief of NCI's Biometric Research Branch.

For example, cancer statisticians primarily developed the methodology that uses patient prognostic characteristics and other data to calculate survival for patients who remain alive at the end of a trial.

"We're very heavily dependent on statisticians," Fisher said. "The statistician also plays a very important role from the beginning . . . to make sure that the trial will answer the kinds of questions that you pose."

The speed of clinical trials has increased in recent years, too. In 1988, NCI established the High-Priority Clinical Trials Program, which in some cases has enrolled patients at six times the average accrual rate for NCI's 180 phase III trials. Trial accrual now averages about 3 years, Chabner said.

Quality Improves

The quality of the trials has also been improved by the training that thousands of physicians receive through participation in studies at comprehensive cancer centers, in the Community Clinical Oncology Program, or in the 13 clinical cooperative groups that conduct most of NCI's phase III trials.

Dr. Michael Friedman

"The answers that are being gained are being gained with greater precision," said Michael Friedman, M.D., director of NCI's Cancer Therapy Evaluation Program. "And so overall, the general mechanism of studying clinical issues is much more efficient than it was 20 years ago."

Today, NCI spends about $2,400 per year for each of the 25,000 patients in treatment on trials. In 1971, Fisher recalls, NSABP was spending less than $200 per year per woman on its breast cancer study.

The National Cancer Act provided for additional basic research and clinical trials in the 1970s. But since 1980, the constant-dollar value of support for the clinical cooperative groups

has decreased by more than 30%, according to NCI figures.

"We're trying to do more with less," said Emil Frei III, M.D., director of the Dana-Farber Cancer Institute in Boston. "And whenever you do that, people are asked to do things for which they're not getting paid, particularly people in practice."

NCI's Chabner agrees: "These people are volunteering their time in many instances." NCI pays for data managers and other costs but regularly runs a deficit of up to $2 million per year in unpaid reimbursements to groups for the costs of putting patients on trial, he said.

Although only 1.5% to 2% of cancer patients now enroll in clinical trials, it is the lack of money that limits the number of patients that can be put on trial.

Screening Trials

Clinical trials have played a role in testing cancer screening methods as well as defining their own limits. The first such study in 1962 showed that screening could reduce death from breast cancer by 30% in women over age 50, said Charles Smart, M.D., chief of NCI's Early Detection Branch.

In the 1970s, a much larger demonstration project without a control group, sponsored by NCI and the American Cancer Society, demonstrated that women would comply with breast cancer screening.

Screening trials begun in the 1970s for colorectal and lung cancers, however, have had problems: many patients in the control groups obtained on their own the same screening given to the study group.

"With screening trials," Smart said, "it's very difficult to try to test and prove anything that is in current use, because you can't get an uncontaminated control group."

Limitations

Screening trials involve healthy subjects, and thousands must be screened to find a statistically significant number of cancers. Screening studies are usually complicated further and made more expensive by the need to follow each participant until death, drawing out the studies 10 to 20 years or more.

An upcoming NCI screening trial for prostate, lung, colorectal, and ovarian cancers is estimated to cost about $83 million. "I believe in [screening trials], but they have problems," Smart said. "We've got to find a better way."

Clinical trials have also been used since 1983 to test chemoprevention strategies. In these trials, people usually are given a substance, such as vitamin C or beta carotene, to prevent the development of cancer.

The first such study to be completed reported in 1990 that a vitamin A analogue prevented new mouth and throat tumors in all but 2 of the 49 patients treated, said Peter Greenwald, M.D., director of NCI's Division of Cancer Prevention and Control.

Gold Standard

"There's no way that we can get strong evidence that cancer is preventable using single specific substances without doing a trial," he said. "The gold standard is a trial."

Later this year, Fisher's group will launch a trial to learn whether anti-estrogenic tamoxifen will keep women with increased risk of breast cancer from getting the disease.

And NCI also is beginning a $7.5-million, 3-year pilot study aimed at getting women to reduce dietary fat and thereby reduce the incidence of breast and colorectal cancers and overall death rate. If the main project is approved, it will be a $107-million, 15-year study of 24,000 women.

"The future is very bright for clinical trials because of the great ideas that are being produced in laboratories, very innovative ideas," Chabner said. "It's just a matter of whether the support will be there for doing clinical research."

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Epidemiology: Uncovering Clues To the Mysteries of Cancer

By Michael E. Newman and Kara Smigel

The way that researchers study the who, what, where, and why of cancer occurrence remains structurally unchanged in the 20 years since the National Cancer Act. But specialization within the field, the advent of large computer databases, and biotechnologic breakthroughs helped the Act give cancer epidemiology a critical push into the scientific fast lane.

Dr. Marvin A. Schneiderman

"We're still concerned with the same problems; we're still concerned with what causes the disease, who develops the disease, and what are the risk factors," said Marvin A. Schneiderman, Ph.D., associate director for the National Cancer Institute's Field Studies and Statistics Program (now the Epidemiology and Biostatistics Program) in the 1970s.

"The National Cancer Act, in an indirect way, made it possible to simply do more epidemiology," he added. "It provided the money by which we were able to get good staff and let them loose to work on what they wanted to work on." Schneiderman is currently senior staff scientist on the National Research Council's Board on Environmental Studies and Toxicology.

More Sophistication

Brian MacMahon, M.D., Ph.D., professor emeritus of epidemiology at the Harvard University School of Public Health in Cambridge, Mass., agreed that the science itself has not changed. "The objectives of cancer epidemiology are still the same and the procedures are, in broad terms, the same. But the level of sophistication is much higher."

With the sophistication came specialization, said Joseph F. Fraumeni, Jr., M.D., current director of NCI's Epidemiology and Biostatistics Program. "In the early 1970s there was a relatively small group of cancer epidemiologists in the United States, and they had limited resources. The NCI group was very focused and clinically oriented."

Cover the Waterfront

The resources provided by the National Cancer Act included an allotment of positions at NCI specifically for epidemiologic research. "The epidemiology group underwent a mitotic cleavage into environmental and clinical sections, covering the waterfront of cancer epidemiology," he explained.

Occupational, radiation, viral, nutritional, genetic, demographic, and statistical research expanded not only within intramural NCI, but elsewhere. "What was happening at NCI was a microcosm of what was going on throughout the United States and worldwide," Fraumeni said.

Specialization of epidemiology in the 1970s made it possible for researchers to wholly consider the multiple factors that cause cancer, said Pelayo Correa, M.D., chief of epidemiology at the Louisiana State University School of Medicine in New Orleans.

"With the increased support provided by the National Cancer Act, we started trying to deal epidemiologically with the many sides of the cancer developmental process—molecular, biological, biochemical, and histological to name a few," he explained.

One advantage to this specialization, added Clark W. Heath, M.D., vice president for epidemiology and statistics at the American Cancer Society, is that epidemiologists are now dealing with more subtle risk factors than in the past.

Dr. Clark W. Heath

Small Relative Risks

"In the 1950s and 1960s, epidemiologists focused primarily on smoking and lung cancer where the relative risks were in the 10- to 30-fold range," Heath said. "Now we're dealing with factors like diet that have relative risks that are only 2-fold or less."

The researchers all said that epidemiology's rapid progress over the past 20 years has been catalyzed by the "increasing sophistication" of the methods and tools available.

Landmarks include advances in case-control and cohort methodology, developing logistic regression statistics for analyzing data with multiple variables, establishing a national cancer database (NCI's Surveillance, Epidemiology, and End Results program), and mapping cancer mortality rates to identify possible "hot spots."

Such improvements went "hand in glove" with advancements in computer technology during the 1970s and 1980s, Heath said.

"For example, the development of large data sets and cancer registries made possible by increased computer capacity has dramatically changed the way we utilize population-based data," he said.

Schneiderman added, "Doing complex statistical computations without computers would be like building the pyramids today by hand. It's possible, but with a crane you can build them faster."

The computer's ability to "share the wealth" has been most valuable, Correa said. "The computer revolution made data collection, statistical analysis, access to population databases, even cancer mapping possible for all epidemiologists," he said.

The wealth of epidemiologic research banked since 1971 has yielded significant payoffs. For example, cancer mortality maps prepared by NCI showed elevated death rates from mouth and oral cancers among women in North Carolina. Subsequent field studies revealed snuff dipping was the primary cause.

Other investigations have been equally productive:

• In the viral field, population studies in Taiwan and mainland China strongly linked chronic hepatitis B virus infection with increased risk for liver cancer.

• Long-term studies of atomic bomb survivors in Japan defined the effects of ionizing radiation on cancer risk.

• Occupational studies have linked work exposures to cancers such as lung cancer in workers exposed to arsenic, and non-Hodgkin's lymphomas and leukemias in farmers working with pesticides.

• Clinical studies showed that some chemotherapy drugs may cause acute leukemias and other second cancers.

• Families with inherited cancers have been tracked and genetic links identified in some

cases, such as with retinoblastoma, Li-Fraumeni cancer family syndrome, and familial melanoma.

• Dietary factors such as fat, fiber, fruits, and vegetables have been shown to influence a variety of cancers.

Prevention Angle

The newest tool for epidemiologists is molecular biology.

"Biochemical or molecular epidemiology came into being thanks to developments in basic research in the cancer field," Fraumeni said. This molecular focus allows better estimates of the subtle, cell-level effects of low-level exposure to carcinogens.

Being able to assess the molecular biology of cancer also moved epidemiology from a greater focus on diagnosed cancers to a prevention angle. "There's more hope for prevention when you understand the precancerous process," Correa said.

"Epidemiology is a necessary first step toward prevention research," explained Peter Greenwald, M.D., Dr.P.H., director of NCI's Division of Cancer Prevention and Control. However, it is only a first step, he said.

For example, while it has been possible to show that fruits and vegetables are protective against many cancers, Greenwald said, the exact active components in these foods are hard to pinpoint via epidemiologic research.

"This kind of specificity requires intervention trials," he stated.

Other Fields Benefit

In addition to the benefits that cancer prevention research has derived from cancer epidemiology, noncancer fields have also reaped the rewards.

For example, the viral epidemiology of cancer was one subdivision of research that, in the 1970s, was not living up to early expectations. However, the viral epidemiologists were there and ready to respond when a different crisis hit in the early 1980s—AIDS, Fraumeni said. "The viral epidemiologists knew what to look for when the AIDS epidemic started. They really hit the ground running," he added.

"It's probably more true of cancer research than most other areas that epidemiology has had a lot of support . . . a great deal more support than it did 20 years ago," said Harvard's MacMahon. NCI's Fraumeni sees the same picture. By the early 1970s, research focusing on high-risk populations and major risk factors led to a greater awareness of the contribution the field had to make. "Epidemiology was now clearly in the mainstream of cancer research," he said.

In recent times, technologic advances have been adopted to facilitate the search for the multiple causes of cancer. "All the easy epidemiology has been done," summarized Sir Richard Doll, M.D., D.Sc., of Oxford University in England.

According to Fraumeni, the next phase of research will require interdisciplinary strategies combining the best efforts of epidemiologists and basic scientists.

"The task ahead is much more complicated," he said.

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Investment in Cancer Research Pays Off for Other Diseases

By Jill Waalen

The National Cancer Act was greeted in 1971 with public expectation of a cure for cancer and a fear in the scientific community that it would be done at the expense of research on other diseases.

Twenty years later, it can be argued that rather than draining other biomedical research efforts, the hefty investment in cancer research paid off in terms of money, treatments, and understanding of basic biology for medicine as a whole.

And as basic research converges on essential cellular processes, the cross-feeding between cancer and other fields continues to grow.

Budget Booster

The National Cancer Act not only boosted the budget of the National Cancer Institute, but of the entire National Institutes of Health, according to Emil Frei, III, M.D., director of the Dana-Farber Cancer Institute in Boston. Frei testified at a recent Senate hearing on the 20th anniversary of the Cancer Act.

"The budget of the NCI moved successfully from $190 million per annum in 1970, to $1 billion in 1980, and the budget of the NIH went from $1 billion in 1971, to $3.5 billion by 1980—proving the best way to get a raise is to have your neighbor get a raise," Frei said.

NCI's drug development machinery turned some of those dollars into treatments that became useful for diseases in addition to cancer. The institute's unique program, in place since the 1950s, enabled it to develop and test drugs of little interest to pharmaceutical companies because cancer was considered incurable at the time, said Gregory Curt, M.D., director of NCI's Clinical Oncology Program.

"It was precisely this program that allowed [NCI Director] Samuel Broder [M.D.] to develop AZT as the only currently approved treatment for AIDS," Curt said.

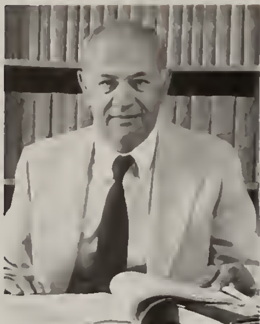
Double-Duty Drugs

The institute's Natural Products Program continues the search, screening 20,000 synthetic and natural products annually for anti-HIV activity.

As the largest repository for therapeutics from natural sources, the program has identified a number of versatile compounds—most recently hydroxyurea, a moderately effective anti-cancer drug first tested clinically in the 1960s and recently found potentially useful for treating sickle cell anemia.

Leukemia research produced immunosuppressants, beginning with methotrexate, for treating autoimmune diseases such as arthritis and graft rejection in organ transplantation.

Curt predicts future cancer spin-offs will include tamoxifen, now being tested as adjuvant therapy for breast cancer. Tamoxifen may protect against osteoporosis and heart disease in postmenopausal women.



Dr. Dani Bolognesi

"No field in biomedicine today stands alone," said Dani Bolognesi, Ph.D., virologist and AIDS expert at Duke University in Durham, N.C. Perhaps the most prominent example is the merging of his own field with cancer research in the battle against AIDS.

"It's hard to imagine where we'd be with this epidemic right now without the support of cancer research," Bolognesi said.

Decipher Communications

Researchers of leukemias and lymphomas long sought to decipher the complex communication between the mixture of diverse cells constituting the immune system. The discovery of the T-cell CD4 receptor and the lymphocyte growth factor interleukin-2, among others, resulted from their efforts. The CD4 receptor was later identified as the docking site for HIV to infect T cells.

With IL-2 in hand, NCI's Robert C. Gallo, M.D., was able to grow lymphocytes in culture and isolate the first retrovirus shown to cause human disease, HTLV-1, in 1978—paving the way for isolation of HIV in 1984.

Indispensable Tools

"The cancer institute was home for retroviral research," Bolognesi said. Initially of interest because they harbored oncogenes, retroviruses are now indispensable medical research tools for gene cloning and as vectors for gene therapy, inserting desirable genes into the chromosomes of patients' cells.

Angiogenesis is another area of overlap between cancer and other diseases. To grow and spread, tumors need to sprout new blood vessels. The process is required for the progression of arthritis and atherosclerosis as well.

Fibroblast growth factor stimulates the growth of endothelial cells which form the new vessels. Judah Folkman, Ph.D., of Boston's Harvard University, pioneered studies on blood vessel growth in tumors and has been a key contributor to the understanding of FGF's angiogenic effects.

Dr. Judah Folkman

Thomas Maciag, Ph.D., discoverer of acidic FGF and head of the laboratory of molecular biology of the American Red Cross, points out that not only could FGF blockers be therapeutically useful, but FGF itself could be used to stimulate desired growth—for example, to repair the fragile blood vessels of diabetics.

FGF is also neurotrophic, with the potential to repair injured nerves, while FGF inhibition has been implicated in Alzheimer's disease.

Transforming growth factor, first described by a cancer research group at NCI that included Michael Sporn, Ph.D., and named for its ability to transform normal cells into cancer cells, has been linked to the development of glomerulonephritis. This scarring of the kidney occurs in diabetes and other diseases. Sporn and colleagues have recently shown that antibodies to TGF beta could prevent the scarring.

The discovery of yet another growth factor, platelet-derived growth factor, exemplifies the serendipity that often links seemingly unrelated fields, Maciag said.

In the early 1980s, NCI researcher Stuart Aaronson, Ph.D., and colleagues were studying the retroviral oncogene sis and its protein product. At the same time, cardiovascular research groups were trying to isolate growth factors involved in atherosclerosis, while others were looking for factors critical to wound healing.

"It was only when the proteins were sequenced that they realized they were all studying the same molecule, PDGF," Maciag said.

Oncogenes

Oncogenes, and anti-oncogenes, in fact, have proved important bridges between cancer and other fields. Historically named for their ability to promote or suppress tumors, the genes have subsequently been found to code for mutant forms of growth factors, growth factor receptors, intracellular signal transducers, and nuclear transcription factors important for the growth and differentiation of normal cells.

"The most exciting regulatory genes important in development have come from two main sources, oncogene research and Drosophila genetics," said Igor Dawid, Ph.D., of the National Institute of Child Health and Human Development. Now those same oncogenes are showing up in the Drosophila genome.

An example is the oncogene *int1*, a retroviral oncogene described by J. Michael Bishop, M.D., and Harold Varmus, M.D., in the early 1980s. A homologous gene in Drosophila was separately identified as the "wingless" gene.

In recognition that they are the same gene, *int1* has been renamed *wint*. The *wint* gene is now known to be critical in the development of amphibian embryos and the nervous system of mice, Dawid said.

The hunt for oncogenes in the human genome

Selected Cancer Spin-offs

Cancer Treatment	Comment	Spin-off
AZT	Activity first demonstrated against mouse leukemia virus	First effective therapy and currently only treatment approved for AIDS
methotrexate	Long used to treat leukemia; prototypefor anti-microbial inhibitors of dihydrofolate reductase	Increasingly used in refractory rheumatoid arthritis, psoriasis
interferon	Potential cancer use spawned Biological Response Modifiers program and recombinant techniques for producing biologicals	Treatment for chronic active hepatitis
OKT3	Monoclonal antibodies developed to identify T cell subsets	Effective in inhibiting graft rejection in renal and heart transplants
trimetrexate	Anti-folate to overcome membrane transport resistance	Effective for refractory pneumocystis and toxoplasmosis in AIDS
cytoxan	Initially used to treat lymphoma	Treatment for vasculitis and membranous glomerular nephritis; Wegener's granulomatosis
immuran, allopurinol	Originally designed and tested for anti-cancer activity	Used for transplants and autoimmune disease

Source: Gregory Curt, M.D., and Bruce Chabner, M.D.

has helped the search for other disease-related genes. The oncogene *met* was used as a marker for the nearby cystic fibrosis gene on chromosome 7, found by two different teams in 1989.

Future Links

New connections between oncogenes and genetic diseases other than cancer continue to be revealed. For example, the products of the *ras* oncogene and the neurofibromatosis gene are thought to interact, suggesting a common molecular mechanism in the development of cancer and the benign tumors associated with NF.

Even more recently *ras* has been linked to an inherited heart disorder called long QT syndrome.

"From my perspective as a virologist, some of the hottest research going on in cancer today is cancer vaccines, singling out some of these genes and vaccinating against them in ways that have been done for infectious diseases," Bolognesi said. "All of this is churning right now." If the past 20 years are an indication, cancer research will end up both beneficiary and benefactor.

Metastasis: Moving Closer Toward Blocking the Spread of Cancers

By Lou Fintor

Newly diagnosed cancer patients and their physicians face a race against time, not only to limit or reduce the growth of tumors, but to block the spread and invasion of cancer cells into healthy body tissues. This spread is what most often leads to treatment failure.

In 1971, no one knew why some cancers spread and others do not. No one knew why some spread more rapidly and aggressively than others. No one knew why some spread almost without exception to the same tissues or organs. And, no one knew how to arrest the process.

This process, called metastasis, was one of cancer's most baffling and deadly mysteries. Today, however, researchers not only understand how cancer cells proliferate and invade, but they are within reach of revolutionary treatments that can restrict cancer cells to primary tumors.

Dr. Isaiah J. Fidler

A Watershed

Isaiah J. Fidler, D.V.M., Ph.D., and colleague Margaret Kripke, Ph.D., were collaborators at the National Cancer Institute 20 years ago, studying the little-understood metastatic process of melanoma in mice. With no way to study the process in test tubes and hampered by the "sheer complexity" of metastasis, frustrations and false leads were common.

Although melanomas often metastasized to the lung, the two researchers found that some cloned tumor cells produced many lung metastases while others did not spread to the lung at all.

The watershed result demonstrated for the first time that cells from a single tumor were highly specialized and vary greatly in their metastatic abilities.

In 1973, Fidler showed that cells isolated from metastases were more metastatic than cells isolated from primary tumors. "That was the first time that [we] had access to cell lines with different metastatic properties isolated from the same tumor," Fidler said.

Metastatic Phenotype

"This immediately allowed studies to determine the metastatic phenotype. However, what these studies did not answer was whether metastatic cells pre-exist in the parental tumor or result from the process of adaptation. The first experimental proof that metastatic cells arise from unique subpopulations contained within the primary tumor came in 1978," explained Fidler, who holds the R. E. Bob Smith Chair in Cell Biology at the University of Texas M. D. Anderson Cancer Center, Houston.

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Complex Process

Scientists now know that the metastatic process is not elementary: first, the primary tumor cells break away individually or in clumps and circulate to distant sites by cleverly traversing a number of extracellular matrixes and dodging other cellular barriers before they can enter their primary routes of transportation: capillaries and the lymphatic system.

In the small vessels of the target organ, the cancer cells adhere to the endothelial lining, causing the endothelium to retract, exposing the more vulnerable underlying subendothelial membrane.

Next, these cells aggressively attach to the basement membrane. Then the endothelium prevents the cells from further circulating by "rolling back" over them. After about 8 to 12 hours, the tumor cell breaks through the basement membrane, exits, and begins growing as a separate colony. Once in place, the tumor cell can be autonomous or locally controlled; it can either produce its own growth factors or respond to those produced by surrounding cells.

Promotes Metastasis

"We assume that in order for a tumor cell to go through these complicated steps, it must possess the right combination of gene products with the ability to invade, overcome host defenses, adhere at the distant site, and grow as a metastatic colony," said Lance Liotta, M.D., Ph.D., chief of NCI's Laboratory of Pathology.

"The research objective is to identify such gene products and how they work," he explained.

When Liotta joined NCI in 1976, Philadelphia researcher Nicholas Kefalides, M.D., Ph.D., at the University of Pennsylvania, had only recently uncovered a new basement membrane barrier protein called type IV collagen. After Liotta learned to isolate the material, he found that tumor cells rapidly attached to it, bore into it, and then migrated through it. It appeared that the tumor cells produce an enzyme allowing them to puncture the membrane and invade. It followed that blocking the enzyme could potentially block metastasis.

According to Liotta, among the many insights gained through the last 20 years, three specific advances illustrate how much progress has been made in battling metastasis.

First, a powerful new enzyme inhibitor, a protein called TIMP-2, was isolated. This was accomplished after scientists encountered difficulties in purifying a tumor cell enzyme that destroys basement membranes because TIMP-2 repeatedly bound to it.

This discovery, by NCI's William Stetler-Stevenson, M.D., Ph.D., opened the door to a new therapeutic strategy in which TIMP-2 or similar drugs could be used to abolish the ability of tumor cells to invade. This new modality could be useful in treating the painful and debilitating bone metastases of breast and prostate cancer patients. It could be used for other purposes as well, including blocking tumors before they invade and spread.

Suppressor Gene Discovered

Second, from a pool of thousands of genes came the isolation of the gene called NM23, by NCI's Patricia Steeg, Ph.D. The discovery of NM23, which acts as a suppressor gene, normally inhibiting metastasis, helped explain why tumors vary in aggressiveness and ability to metastasize.

Later research by scientists in Japan and Great Britain supported the NM23 theory. One breast cancer study showed that women with high NM23 levels lived much longer than those with low levels.

Researchers hope that relatively soon NM23 can be used as a prognostic marker in node-negative breast cancer. Because about 25% of these patients harbor undetectable metastases that will ultimately lead to death, measuring NM23 levels might help physicians identify high-risk patients for more aggressive treatment.

Eventually, by understanding NM23's full

mechanism of action, researchers might develop a new anti-cancer drug that could mimic its effects.

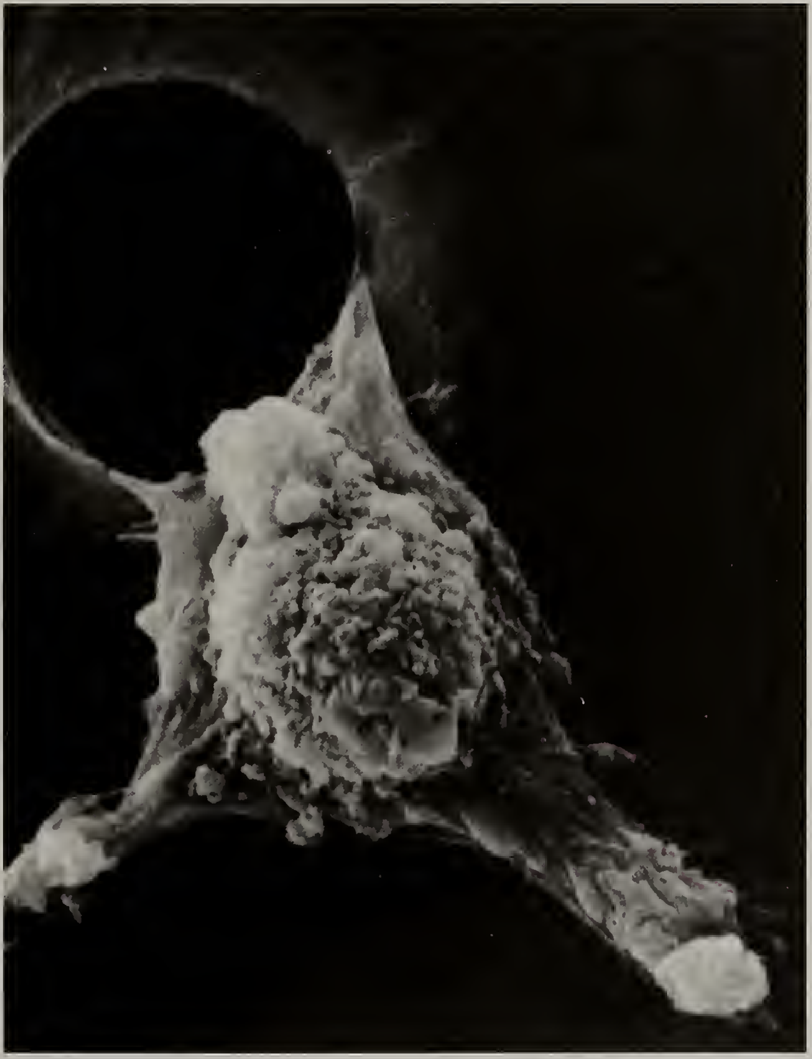
Shows Promise

Third, by examining the "crawling" process by which cancer cells move and invade, investigators found in 1985 that the *ras* oncogene promotes the rapid movement of benign cells by responding to specific biochemical pathway signals that had been "turned up like the volume on a radio." Scientists began screening for drugs that could block the pathway.

After hearing about an abandoned research drug that had been developed to treat chicken parasites and appeared to affect a similar biochemical pathway, Elise Kohn, M.D., and a team in NCI's Division of Cancer Treatment, found that the drug not only overwhelmingly halted tumor cell invasion but even inhibited tumor cell growth. The drug, which they named "CAI," has been used successfully in the last few years to halt the growth of more than 20 different types of human cancer cells, including breast, colon, prostate, ovarian, and melanoma.

In animals, CAI stops and can reverse the growth of transplanted human cancer cells in both primary tumors and metastases. In addition, it appears to have little toxicity.

With a CAI government patent application in hand, a team of NCI researchers will attempt to bring this "completely new approach to cancer treatment" to phase I clinical trials this fall.



A metastatic cancer cell extends pseudopodia to move through cellular membranes.

Liotta attributes rapid scientific progress in understanding and developing treatment modalities for metastasis to the increased funding and interest stimulated by passage of the 1971 National Cancer Act.

"In 1971, the clinical significance of metastasis was appreciated, but very little was known about what caused cancer cells to metastasize," Liotta recently told the U.S. Senate's Labor and Human Resources Committee.

"To tackle the problem, investigators have separated invasion and metastasis into a series of defined sequential steps, and focused on one step at a time using the latest molecular techniques," he explained. "We now have in our hands some of the genes and proteins that regulate the cancer process. With the help of these tools, we will undoubtedly be able to generate a host of new approaches to attack cancer."

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1971-1991: Molecular Oncology Comes Into Its Own

By Elaine Blume

When the National Cancer Act was signed in 1971, the cancer cell was a black box. Scientists had learned a few important things about the inner workings of the normal cell, but their information was rudimentary, and most of it was based on bacterial rather than mammalian cells.

Today, the black box has been opened to reveal a crude but informative road map. Portions of the map remain blank, but these parts are being filled in at a rapid pace.

"We have identified some of the major differences between normal and transformed, or tumorigenic, cells," said George Vande Woude, Ph.D., director of the ABL Basic Research Program at the National Cancer Institute's Frederick Cancer Research and Development Center in Frederick, Md. "The picture of what happens, all the way from extracellular signals, right through until the cell divides, is beginning to really fill in."

Not Much Known

Back in 1971, the most interesting and important thing biologists knew about cells was that DNA carried the vital inherited blueprint for the cell's proteins and directed synthesis of these proteins through the mediation of RNA.

Virology had become an area of particular research interest for basic biologists, because it was known that when viruses infected cells, they took over the cells' genetic machinery. Thus, viruses seemed to offer a handle with which to gain insight into the working of cells.

Scientists also knew that some viruses produced tumors in animals. Because of this, many speculated that viruses might be an important cause of cancer in humans as well as animals.

This theory was appealing for several reasons. First, it relied on a disease model with which everyone was familiar. Viruses caused measles, smallpox, encephalitis, and an array of other diseases. Why not cancer as well? Also, the fact that viruses commandeered the genetic machinery of infected cells fit well with the general belief that cancer resulted from genetic changes in cells.

Hope for Solution

Finally, the virus theory of cancer offered hope of a rapid solution. Many viral diseases had been effectively combated with vaccines. Perhaps cancer could be dispatched with similar ease.

Still, if viruses were at the root of many human cancers, they appeared to be viruses with a difference. A variety of biological insults, including x-rays and certain chemicals, could

reliably be used to produce cancer in animals. What role might viruses play in such tumors? Did many or all cells contain latent viruses that needed only x-rays or chemicals to become active and give rise to cancer?

Some scientists thought the answer was yes, and they proposed theories postulating the existence of such near-universal "viruses" embedded in the genetic material of cells. The oncogene hypothesis of the National Cancer Institute's Robert Huebner, M.D., and George Todaro, M.D., was one such theory. The protovirus (or provirus) hypothesis of Howard Temin, Ph.D., of the University of Wisconsin, was another.

Reverse Transcriptase

But in 1970, the attention of cancer researchers again focused on viruses external to cells. Temin and his colleagues at Wisconsin, and independently, David Baltimore, Ph.D., and his co-workers at the Massachusetts Institute of Technology, discovered that a unique enzyme was present in certain RNA tumor viruses of animals, such as Rous sarcoma virus.

This enzyme, reverse transcriptase, whose existence had been predicted earlier by Temin, used the RNA genomes of these tumor viruses (subsequently known as retroviruses) as templates for synthesizing DNA, thus reversing the usual flow of genetic information from DNA to RNA to protein.

Reverse transcriptase, scientists reasoned, could be the link between RNA viruses and cancer. The enzyme could copy cancer genes from viral RNA into DNA, and this DNA in turn could become integrated into the cellular genome, permanently transforming the cell. Researchers went to work at once, trying to identify cancer genes in tumor viruses.

Viral Oncogenes

Within a few years, scientists succeeded in identifying the cancer-causing *src* gene of Rous sarcoma virus and its protein product as well. The src protein, which goads previously normal cells to the unconstrained growth of cancer cells, eventually proved to be a tyrosine kinase—an enzyme that specifically phosphorylates (adds phosphate groups to) the tyrosine subunits of proteins.

While other researchers busied themselves identifying additional cancer-causing genes, J. Michael Bishop, M.D., Harold Varmus, M.D., Dominique Stehelin, Ph.D., and their colleagues at the University of California School of Medicine in San Francisco, used *src* to test Huebner and Todaro's oncogene hypothesis.

Stehelin made radioactive probes of *src* DNA by copying the viral *src* gene from RNA to DNA with reverse transcriptase. He and his colleagues then used these probes to search for sequences similar to *src* in the DNA of normal cells.

The search proved successful. In 1976, the researchers found *src* sequences, first in the DNA of uninfected chickens and other birds, and later in mammals. Although the discovery appeared at first to support the oncogene hypothesis, subsequent work made it clear that this hypothesis had failed to hit the mark.

Altered Genes

Cellular oncogenes like *src*, scientists concluded, are not latent cancer viruses. Rather, they are normal cellular genes that are present and active in normal cells. These genes produce cancer only when they, or their regulators, have been altered by mutation.

"For example, some oncogenes normally work only at one very specific place in the cell cycle," Vande Woude explained. "But when such an oncogene transforms cells, we find that it is being actively expressed throughout the cycle. The transforming mutation has brought about this change."

Scientists studying the subject concluded that the presence of oncogenes in viruses was coincidental. As retroviruses evolved along with their host cells, they apparently copied these (and other) cellular genes and added them to the viral genomes. When oncogenes re-enter the

cell as part of the virus, they may behave abnormally and this aberrant behavior can lead to cancer.

As evidence grew that oncogenes had originated in cells rather than in viruses, researchers began trying to isolate transforming genes from mammalian tumor cells.

In 1979, research teams led by Robert A. Weinberg, Ph.D., of MIT, Geoffrey Cooper, Ph.D., of Harvard Medical School, and Michael Wigler, Ph.D., of Cold Spring Harbor Laboratory, independently succeeded. Like retroviral oncogenes, these mammalian oncogenes proved to be closely related to genes that were present and active in non-cancerous cells.

Suppressor Genes

Meanwhile, independent lines of work by Alfred Knudson, Jr., M.D., Ph.D., of the Fox Chase Cancer Center in Philadelphia, in 1971, and by Henry Harris, M.D., of Oxford University, a few years earlier, had led scientists to believe that normal mammalian cells contained genes that restrained the cells' growth, and that loss of these genes could lead to cancer. These putative tumor suppressor genes appeared to act recessively, unlike oncogenes, which produced cancer in a dominant fashion.

In 1986, MIT's Weinberg, along with Stephen Friend, M.D., Ph.D., and their colleagues, cloned a gene, *RB*, whose absence was linked with retinoblastoma and other cancers.

Subsequently, Wen-Hwa Lee, Ph.D., of the University of California at San Diego, showed that when *RB* was inserted into human retinoblastoma and osteosarcoma cells in culture, the cells lost their tumor-forming capacity. Tumor suppressor genes (also called anti-oncogenes) now had a solid place in the schemata of carcinogenesis.

The Big Picture

Work in very recent years has fleshed out these findings. Oncogenes have been found to play a variety of roles in cells. Some act as receptors for growth factors, or as "second messengers" in signal transduction; others regulate transcription of DNA into RNA. Several may play a direct role in progression of the cell cycle. Tumor suppressor genes may act at many of the same sites as oncogenes, though with an opposite effect.

Scott Kern, M.D., Bert Vogelstein, M.D., and their colleagues at The Johns Hopkins University School of Medicine recently reported that the protein product of the tumor suppressor gene *p53* binds to a specific sequence of human DNA. In addition, the researchers found that mutated forms of *p53* commonly occurring in human tumors produce proteins that lack this binding ability. These results indicate that *p53*'s role as a tumor suppressor may be mediated by specific DNA binding. Work of these and other investigators suggests that this DNA binding may influence the cell cycle.

The transforming proteins of some DNA tumor viruses have been shown to complex with the protein products of cellular tumor suppressor genes; such complexes may block activity of the tumor suppressors. Peter M. Howley, M.D., of NCI, has found that, in one case, the complex actually results in degradation of the tumor-suppressing protein.

Generally, cells must undergo several genetic changes, typically involving both oncogenes and suppressor genes, to become fully malignant. Several groups of scientists have tracked these changes as cells gradually move from normal to cancerous. Slowly, an all-but-complete picture of cancer development has emerged.

"Now," Vande Woude said, "in terms of understanding mechanisms, I think we're very, very close. And the most revealing findings have just come in the past several years."

This augurs well for medicine's future ability to prevent and treat cancer. But Vande Woude sees broader implications in the new knowledge.

"The most spectacular thing that's happened in the past decade is showing that even after one billion years of evolution, you can take a human gene and put it into yeast, supplanting a homologous gene, and the yeast will grow and

divide," Vande Woude said. "That means the function of that [gene] product has been conserved over a billion years.

"Those conserved genes are the genes that are causing cancer. But that is not why they are there. They are there because they are so fundamental to biological processes. If you knock one out, that's the end of life."

1971-1991: Quality of Life Gains Increased Attention

By Francis X. Mahaney, Jr.

In the 20 years since the National Cancer Program was established, quality of life has markedly improved for millions of Americans with cancer. Cancer patients are now living longer, more active, productive lives.

New treatments enable patients and their physicians to choose from a range of procedures that restore the patient's health with fewer side effects.

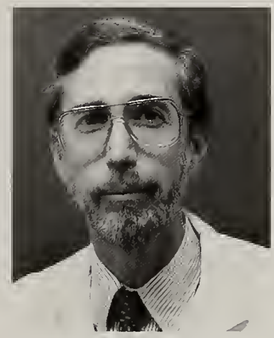
Recent advances in plastic surgery enable many patients to live without the same physical and emotional consequences cancer patients faced in 1971.

No longer must cancer patients confront their disease alone. Through support groups and patient education, patients can share their feelings, make clearer decisions regarding treatment, and respond to life more fully.

Consider these advances:

- Patients with laryngeal cancers can be treated successfully with radiation treatments with full preservation of the voice.
- For patients with osteosarcoma, segmental bone resection plus endoprosthesis has replaced amputation, in many cases.
- In bladder cancer, neo-adjuvant chemotherapies followed by radiotherapy are being evaluated as an alternative to cystectomy.
- In colorectal cancer, new surgical techniques have eliminated the need for ostomies in many patients. Now only 15% of these patients require a permanent ostomy.
- Nerve-sparing lymphadenectomy has also been shown to preserve fertility for men with testicular tumors.

Martin D. Abeloff, M.D., new president of the American Society of Clinical Oncology, said, "Looking back to 1971, I am really struck by a real explosion of information that has taken place.



Dr. Martin D. Abeloff

"Not only have we gained tremendous knowledge of the biology of cancer," he added, "but our ability to develop a variety of humanistic therapies and concepts has markedly improved, giving cancer patients more autonomy with a variety of treatment options. Patients now play an active role in the treatment process."

Cultural Shift

Abeloff, who is also clinical director of The Johns Hopkins Oncology Center, Baltimore, said that a major cultural shift has taken place in how the patient and doctor view cancer. That shift enables oncologists to see patients in the first stages of their disease, sometimes even

before a diagnosis of cancer has been reached, so proper treatment can be given at the earliest opportunity.

"For some patients, improvement in disease-free survival can be a surrogate for improvement in the quality of life," said Joyce A. O'Shaughnessy, M.D., of the National Cancer Institute. "This is because oftentimes when breast cancer or other cancers recur they can be symptomatic, and so, prolonging the time to recurrence keeps people symptom free longer."

A major revolution has occurred in the surgical treatment of breast cancer. Since the early 1970s, surgeons have shifted from the disfiguring Halsted radical mastectomy to less extensive procedures often combined now with adjuvant therapy and breast reconstruction.

Dr. Bernard Fisher

Breast Cancer

Spearheading this movement was Bernard Fisher, M.D., of the University of Pittsburgh, who in 1985, with researchers from 89 other institutions, announced that less disfiguring surgical procedures such as lumpectomy (removal of just the cancerous lump) followed by radiation were as effective as removal of the entire breast for many women with early stage breast cancer.

That work ushered in a new era of breast cancer surgery, which improved the quality of life for patients.

"Certainly, in terms of cosmetic results, the use of lumpectomy has given women with breast cancer a greater sense of self-esteem," Fisher said. "From a surgical point of view, there are fewer infections, fewer complications, such as the swollen arms that I saw when I was a young surgeon years ago, and hospitalization times have been lessened," he said.

Fisher believes that because the quality of life for breast cancer patients is better, women are less fearful of undergoing breast cancer surgery than they were two decades ago, and their cancers are being detected earlier. This is also true for other cancers.

Prostate Cancer

"I think as a result of changes in surgical technique and morbidity, more men are getting diagnosed and treated for prostate cancer earlier," said Patrick C. Walsh, M.D., a surgeon at Johns Hopkins University. "And that sure is changing the quality of life."

Walsh said that during the 1970s, "it wasn't uncommon to have a prostate patient bleed to death on the surgical table. Now prostate surgery is much safer, causes less blood loss, and there are fewer side effects."

In 1986, Walsh modified the technique of radical prostatectomy so that today it is possible to "preserve sexual function in the majority of patients and to ensure urinary continence in virtually all."

Also contributing to better life quality has been the development of chemotherapeutic analogs that have made cancer treatment less toxic.

As newer high-dose chemotherapies were developed, scientists increasingly worked to counter significant side effects. Now the armamentarium for the 1990s includes drugs that can prevent the cardiac side effects of high-dose doxorubicin, rescue agents that can prevent damage to healthy cells, and colony-stimulating factors used to alleviate many of the hematologic side effects of chemotherapy.

Less Cardiotoxic

Analogs like the anthrapyrazoles, for example, "which look very promising for the treatment of leukemia and breast cancer," appear to be less cardiotoxic than the familiar anthracycline standby doxorubicin, O'Shaughnessy said.

In breast cancer, "a wide range of endocrine treatments can provide significant benefit with little toxicity for both younger and older women

with less aggressive types of metastatic breast cancer," Abeloff added.

In turn, improvements in pain relief and anti-nausea medicines were made.

Technological advances for pain control include computerized infusion pumps that enable physicians to deliver the proper amount of pain medicines to the patient and can even be self-administered at home, with built-in controls to prevent an overdose of medicine, said Stuart Grossman, M.D., of Johns Hopkins.

Dr. Stuart Grossman

Pain relief can be administered a number of ways. Doctors can now inject narcotic medicines under the skin, in the veins, in the epidural space between the backbone and the spinal fluid that surrounds the spinal cord, and into the spinal fluid itself.

Skin Patch

Other narcotic preparations have been developed to deliver medicine from a patch applied to the skin, Grossman said.

Twenty years ago, cancer patients also died of starvation (or cachexia), from bleeding disorders, and from serious infections that suppressed the body's immune system.

Now, by giving essential nutrients intravenously, the health of the cancer patient has vastly improved, said Emil Freireich, M.D., of the University of Texas M. D. Anderson Cancer Center, Houston. New antibiotics and new technologies to deliver blood platelets have allowed advanced cancer patients to stay healthier for the duration of their cancer treatment, he said.

Late Side Effects

But while there have been some improvements in cancer treatments, there have been some paradoxes as well.

Scientists now have identified late side effects to many of the treatment advances of the 1970s and 1980s.

"Some young women who had once been treated with doxorubicin for their cancers in childhood began to develop congestive heart failure during pregnancy; some patients treated for childhood cancers began to suffer from second cancers, and some experienced treatment-related fertility problems," said NCI scientist Marc Horowitz, M.D. "Other patients suffered from psychological problems, and some still cannot get jobs or medical insurance," he added.

"In this coming decade, we will be taking a good hard look at these problems [with the aim of] improving the quality of life," Horowitz noted.

Samuel Broder, M.D., NCI director, has said that "the patient's definition of 'quality' should outweigh all other measures. This is an issue that involves both informed consent and informed self-evaluation."

He added that one of the key issues to improving the quality of life for a cancer patient "may be adequate information and informed choices—a sense of self-determination."

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Cancer Out of the Closet: Support Emerges Over Two Decades

By Julie A. Steele

Diagnosed with breast cancer in 1968, Georgia Photopulos sought support and information about her disease. She and her husband found that "Our opportunities to talk about this stress, to find ways for dealing with it, were practically nonexistent."

Georgia Photopulos

Dr. Judith Johnson

Judith Johnson, Ph.D., is co-founder of the American Cancer Society's *I Can Cope* program, which began in 1977. "It was very difficult to identify any structured educational programs in the 1970s." Written materials for patients were limited; educational materials were written for health professionals.

Johnson remembers a lot of excitement in 1978 over *Make Today Count,* a patient education program for coping with cancer and other life-threatening diseases. "This was very innovative and new," she said.

"There are numerous educational materials now," Johnson added, "specifically written and tested for various reading levels and numerous kinds of support groups." The types of books available about cancer have changed, too, according to Johnson.

"Early books were mostly personal accounts, and [the authors] died. Books now are more about personal empowerment. They give patients options." There is a movement toward self-care.

Little Hope

"Stories in the 1970s about cancer patients such as Nat King Cole, Brian Piccolo, and John Wayne , always ended with the hero's death," Photopulos said. "They are very poignant and emotional stories, certainly, but filled with despair," she said, offering people "plenty to cry about, little to take hope in."

Photopulos has written about her experience in *Of Tears and Triumphs,* a "guidebook to educate professionals, caregivers, and family members on the emotional needs of cancer patients."

During the early years of her 20-year struggle with cancer, Photopulos found few opportunities to deal with the fear, anxiety, and distress her illness brought. In response, she organized a

24-hour-a-day telephone service for patients and their families in June 1973. Photopulos also assisted in establishing the National Cancer Institute's nationwide toll-free Cancer Information Service.

Pat Fobair, clinical social worker at Stanford University Medical Center, sees the American Cancer Society as a major force behind the change. "ACS raised issues and stimulated action and awareness of early detection, as well as provided professional education," she said.

"No doubt there's been a big change," said Marion Morra, assistant director of the Yale University Comprehensive Cancer Center, New Haven, Conn. Morra said she had a hard time getting on television shows in the 1970s to promote *Choices*, a book for cancer patients she co-authored with her sister, Eve Potts.

Improved Prognosis

In 1990, however, when their second book *Triumph* was published, "people were willing to talk about it. We had none of those problems." Morra feels part of the willingness to talk about cancer now is improved prognosis. "We are able to say 'cure.' In the 1970s, no one was talking cure.

"The media have played an enormous role," she said. "There has been an explosion in information. Few newspapers had health reporters; now there is a health reporter in every major newspaper. People want to hear and discuss health." The result is a more informed, sophisticated population, she added.

Morra, who is coordinator of the Connecticut Cancer Information Service, said information specialists are spending more time on the telephone with callers because people are asking more complex questions.

Leadership of prominent cancer patients in the 1970s and 1980s was a strong force, Fobair said. "Rose Kushner galvanized medical and consumer issues." Kushner, a well-known breast cancer patient and advocate, died in January 1990.

Living with Cancer

"In the 1980s, we saw the emergence of the educated consumer," said Katherine Crosson, chief of NCI's Patient Education Section. Information in the early 1970s was limited to basic treatment, she said. "The emphasis now is on the psychosocial piece—how you live with cancer."

The 1980s have also seen the emergence of groups such as the National Coalition for Cancer Survivorship and Cancervive, offering support to their members and beginning to address issues such as discrimination.

Bill Soiffer

"Cancer is coming more out of the closet," said Bill Soiffer, NCCS member and author of *Life in the Shadow,* which documents, through stories of people with Hodgkin's disease, the extent to which cancer survivors feel stigmatized. Doctors wouldn't discuss a diagnosis of cancer with patients in the 1930s, 1940s, or 1950s, Soiffer said. "In the 1960s, things began to change."

Stigma Diminishing

A 15-year survivor of Hodgkin's disease, Soiffer said the impact of having cancer is slowly diminishing, partly because of the AIDS epidemic. "It has displaced some of the stigma." In the past when people would say, "What is the worst thing I could get?" they would think of cancer. Now, he said, AIDS is more of a death sentence. "One-half of those diagnosed with cancer today will survive," Soiffer said.

Though diminishing, Soiffer said "the cancer stigma lives on." He cited the fact that one in four cancer survivors faces job discrimination; and one in four can't get adequate health insurance. He feels the media perpetuate the stigma of cancer by "hyping human tragedy," such as Michael Landon's death from pancreatic cancer, and paying little attention to stories like that of Paul Tsongas, retired U.S. Senator from Massachusetts and 8-year survivor of non-Hodgkin's lymphoma, who recently announced his candidacy for president.

Barrie Cassileth, Ph.D., said the cancer stigma still exists among the elderly, but the younger generation's views are replacing the old views. The older generation grew up in a time when cancer was not discussed. "The word cancer was not allowed in print. It wasn't even included in obituaries," she said.

During the 1970s and 1980s, Americans also witnessed great biomedical advances, which allowed scientists to prolong life artificially. Cassileth explained that these changes raised a number of issues, like living wills and when to stop treatment. Before this time, discussions of death, cancer, and cancer treatment were taboo. "Now you can hardly pick up a magazine and not find an article on cancer," she said.

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1971-1991: Consumerism Grew As Cancer Became a Curable Disease

By John Burklow

Richard Bloch

Americans today are taking a bolder attitude toward cancer than they did 20 years ago. They are demanding more information, and taking more responsibility and action in all areas of cancer.

"The biggest single thing that has changed in the last 20 years is the attitude that cancer was an unmentionable. Today, it is discussed," said former cancer patient Richard Bloch. He is co-founder of H & R Block, and founder of Cancer Hotline, an information service in Kansas City, Mo.

Newspaper and magazine articles on patients' right to know made a difference, said Irving Rimer, former vice president for public relations for the American Cancer Society. He added that "the interest in breast cancer was spurred on in 1974 by Betty Ford and Happy Rockefeller openly acknowledging their breast cancer."

"Cancer patients have caught on to the fact that they have a chance for cure—they do not see it as a death sentence," said Michael Van Scoy-Mosher, M.D., a medical oncologist in Beverly Hills, Calif., for 23 years. "And they're more often cured without radical procedures such as mastectomy or losing a limb. People come to me much more hopeful than they did 20 years ago."

Universal Instinct

A major change since 1971 has been the tremendous growth of information about cancer. "The most universal instinct in patients is to run to the bookstore or library for more information," said Fitzhugh Mullan, M.D., volunteer chair of the National Coalition for Cancer Survivorship.

"Cancer patients want to know," said Mullan, who also is an assistant U.S. Surgeon General. "They want the information. At the very least, they want to be knowledgeable participants in their cancer care. Some want to be active participants, applying information to make decisions."

Advice columnist Ann Landers said, "People are reading about cancer more now, and they're doing something about it rather than sitting

back. This has come from getting good information. They're much better informed than they were 20 years ago."

Although cancer is still viewed as a dread disease, there is more hope now, Landers added. The key is early detection, she said, not just for breast cancer, but for many types of cancer, and "this is what I try to bring out in my column."

Physicians, too, are seeking more information, according to Bloch. "Twenty years ago, there wasn't as much information on cancer, and most cases were fatal. Physicians now realize that cancer can be treated successfully, and that they need to know about the recent advances made in treatment."

The number of cancer support and service organizations available to patients has grown remarkably since 1971, according to Mullan. There are many groups, including Candlelighters, Reach to Recovery, CanSurmount, Vital Options, all of which started in the community.

New Opportunities

"There are now places I can refer patients to. It increases their awareness, but also their demands. They have the opportunity to share and learn what other patients are experiencing," Van Scoy-Mosher said.

Patients' attitudes and behaviors have changed dramatically over the last 20 years. "Many patients today realize that they are entitled to run their lives," Bloch said. Twenty years ago, they listened to a doctor without question. Today, people think, "I'm paying his or her fee, so I have a right to quality care, to a second opinion."

In 1971, many physicians may have viewed second opinions as a nuisance, or a threat to their knowledge and integrity. Today, many physicians would rather have satisfied patients, Bloch said. "I think they are more likely to welcome a second opinion."

Require Second View

The rise in health care costs helped influence the practice of getting a second opinion, according to Terry Lierman, who staffs the National Coalition for Cancer Research. "We're taught, indeed required by some insurance companies, to seek a second opinion. I think this is a fundamental change."

Patients sometimes seek out multiple opinions, according to Van Scoy-Mosher. "My patients usually seek out two to three opinions, and I had one get eight. They also consult multiple cancer centers."

The area where patients' attitudes and behaviors have changed most remarkably is breast cancer, according to Arthur I. Holleb, M.D., chief medical officer of the American Cancer Society from 1968-1988.

Amy Langer

Treatment choices and options for breast cancer patients have grown tremendously within the last few years, according to Amy Langer, executive director, National Alliance of Breast Cancer Organizations. "People have to wind their way through a complicated maze of decisions after a breast cancer diagnosis."

As a result, support groups expanded rapidly to help meet the information demands of breast cancer patients, Langer said.

The National Alliance of Breast Cancer Organizations was started 5 years ago by the late Rose Kushner, undoubtedly the best known consumer advocate in breast cancer; Nancy Brinker, founder and chair of the Susan G. Komen Breast Cancer Foundation; Diane Blum, executive director of Cancer Care, Inc.; and Ruth Spear, author and editor of *NABCO News*, Langer said.

"She single-handedly changed the 1-step procedure to a 2-step procedure. When she was diagnosed in the early 1970s, she shopped until she found a physician who agreed not to automatically perform a mastectomy if he found

Ann Landers

cancer. It was not common then. It's standard practice now."

In early 1991, eight groups organized the Breast Cancer Coalition, which grew out of a push from grass roots groups around the country. The coalition is now made up of more than 130 organizations.

"The AIDS movement inspired the Breast Cancer Coalition," Langer said. "We saw other patients having an impact. There was a great deal of anger, frustration, and concern. There was a momentum to turn this anger into productive activities. To turn personal experiences into affecting policy for women everywhere."

The coalition has been successful, according to Robin Lipner, professional staff member for Sen. Brock Adams (D-Wash.). For the first time, the Senate Appropriations Committee approved an additional $30 million for breast cancer over the president's budget for fiscal year 1992, she said.

Biggest Mail-In

In 1971, consumer activism on the political front helped force passage of the National Cancer Act. In April that year, Ann Landers urged her column's readers to write their senators to help pass the Conquest of Cancer Bill.

In her column, Landers pointed out that the United States had never had a national campaign against cancer and that research funds were grossly inadequate, especially compared to defense.

"It turned out to be the biggest mail-in to Congress in history, producing over 1 million letters," Landers said. "It hit people where they live."

In 1991, there is a new push from the community for more money for cancer research. "There is nothing more effective than writing your congressman," said Alice Fordyce, board member, Albert and Mary Lasker Foundation. "People are coming to realize that money is not falling like manna from heaven. The federal government has more money than any philanthropist."

Sign of Progress

And, in 1991, with more than 7 million cancer survivors, there is a new push from cancer patients too. "Now, cancer patients are consumers," Rimer said. "They are articulate and are standing up for their rights" for employment, access to insurance, and other critical issues.

He added that the creation of the National Coalition for Cancer Survivorship provided, for the first time, an organization of cancer patients themselves. "You could only have that from successful treatment. It is one of the best signs of progress."

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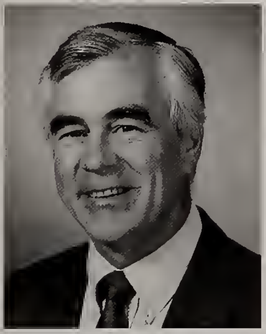
New Diagnostics Unveil Cancers By Visual and Molecular Means

By Cori Vanchieri

Diagnostic imaging has progressed in 20 years to reveal minute tissue densities and metabolic processes. At the same time, molecular analyses are unveiling genetic and molecular changes that may disclose a tumor's aggressive potential.

In 1970, diagnostic imaging relied on two-dimensional x-rays, television-viewing fluoroscopy, and basic nuclear medicine to produce anatomic images. Ultrasound only provided black and white images—no gray scale.



Dr. William Hendee

Then in 1971, computed tomography was introduced. "CT began a revolution in diagnostic imaging," said William Hendee, Ph.D., senior associate dean and vice president, Medical College of Wisconsin, Milwaukee.

CT ushered in the use of mathematical analyses and computers to generate cross-sectional x-rays that revealed very fine, minute changes in tissue densities. With these computers, cross-sectional images were combined to construct three-dimensional images. "We now had a method to visualize the tissues of the brain," Hendee said.

Internal Architecture

"For the first time, [cross-sectional imaging] has given us a detailed look at the internal architecture and margins of tumors," said Richard Steckel, M.D., head of the UCLA Jonsson Comprehensive Cancer Center, Los Angeles. Before, there was only indirect evidence of a tumor's presence. For example, he said, a GI series would show displacement of the stomach or duodenum, only implying the presence of a large pancreatic tumor.

The cross-sectional images could, in a sense, move out of the way organs that were obscuring the tumor on a regular x-ray. Diagnostic imaging was now comparable in some cases to anatomical dissection.

"The new imaging techniques are influential in helping with primary diagnosis of tumors, staging, and post-treatment follow-up to find tumor regressions, recurrence, or second malignancies," Steckel said.

Inconceivable Earlier

The precision of today's techniques enables scientists to externally guide stereotactic biopsy and treatment devices to the tumor site, said David Bragg, M.D., chairman of the Department of Radiology, University of Utah School of Medicine. This has allowed treatments of central nervous system tumors that were inconceivable prior to 1970.

Magnetic resonance imaging was introduced about 10 years after CT. MRI uses a powerful magnet and radiowaves to produce even better soft tissue contrast than CT. By 1985, most academic institutions had at least one MRI scanner. While CT scanning has probably reached its peak, MRI is still in a rapid growth phase, Steckel said.

"We're not close to seeing a plateau of this technology," Stanley Baum, M.D., chairman of radiology, University of Pennsylvania, said in a recent lecture. Scientists are using balloons with surface coils inside, enabling them to bring the coils closer to the organ being observed.

For example, a balloon can be inserted into the rectum to view the prostate. Views are almost microscopic in definition, Baum said. The ductal structures that form the prostate can be defined, and staging of prostate cancer can be accomplished.

Metabolic Data

Out of CT technology also evolved use of special isotopes to emit positrons that can be picked up on a scan. Positron emission tomography looks at metabolism of the tissues. For example, rapidly dividing cancer cells metabolize glucose more rapidly than normal tissue. This high metabolism shows red on a PET scan. PET is quantitative and functional versus anatomical, Baum said.

"We are learning to understand metabolic processes—refining what metabolic abnormalities occur and understanding the specific tissue signatures," said Bragg, who is a member of the National Cancer Advisory Board. Other compounds are being studied along with glucose. For example, sodium is showing promise as a marker for tumor recurrence, according to Bragg.

Researchers have refined PET and can now determine if post-treatment symptoms are due to the injury caused by treatment or due to a recurrent tumor.

Radiolabeled monoclonal antibodies are being used to pinpoint the spread of metastatic tumors. The antibodies collect wherever the cancer has spread, and pass through the body if no cancer is present.

Hendee said that in the mid 1970s the addition of gray scale to ultrasound yielded much better tissue differentiation. Ultrasound works well to differentiate between cysts and solid masses, is widely used to scan the abdomen, and is usually the first test done for undefined symptoms.

X-ray technology also improved. Bragg said that, for example, mammography resolution has improved at a fraction of the x-ray dose used in the early 1970s. The challenge, he said, is to convince women and their physicians of the importance of this exam.

Next Steps

"We need to concentrate more on how to [evaluate] patients after treatment," Steckel said. "There's an enormous amount of misuse of diagnostic imaging in the post-treatment phase because we don't know enough about what are useful studies. What is the periodicity? What is the effect upon the patient?

Dr. Richard Steckel

For example, he said, a stage I breast cancer patient who has a lumpectomy has a low chance of recurrence. But 85% to 90% of these women get annual x-ray scans of the bones and chest x-rays every 6 months. "Is this cost-effective and good for the patient?" Steckel asked.

Limitations

"We still need a better way to image the abdomen," Bragg said. MRI has its limitations. Because of all of the motion in that area of the body, fast imaging is needed. "And we always need to pick up problems earlier," he continued. "We still can't do much for the pancreas."

Steckel added that "these new techniques are extraordinarily sensitive to picking up masses of 1 cm or larger and defining extent of tumor growth, but they are probably not as specific as we would have hoped."

Once the mass is found, he said, they are not good at telling what the mass is. A CT scan can show the presence of a lump, but it usually cannot identify the lump's nature. A tissue biopsy is needed for a definitive diagnosis of the mass. Researchers in molecular diagnostics hope one day to solve that problem. This technique, still in its infancy, may pick up gene alterations that are specific to different diseases.

"It depends on our understanding the biology and knowing what genes to look for," said Sheila E. Taube, M.D., chief of NCI's Cancer Diagnosis Branch. "Given that, the technology has advanced so rapidly that we have capabilities I wouldn't have predicted 8 years ago." Recombinant DNA and polymerase chain reaction have opened up this field (see News, *J Natl Cancer Inst,* Jan. 2, 1991).

Although the technology is not here yet, Taube sees a future in which very sensitive molecular techniques could distinguish between benign and malignant disease. Researchers could also look for genetic alterations that predict whether a tumor will be aggressive, or if it has metastasized. These answers will help clinicians decide how extensively and aggressively to treat a patient.

For example, *N-myc* amplification has been proven valuable in diagnosing neuroblastoma. "Even lower stage tumors that show amplification of *N-myc* have worse prognoses," Taube said.

One diagnostic test of gene rearrangement in the Philadelphia chromosome has been approved by the Food and Drug Administration. This allows molecular identification of chronic myelogenous leukemia. Cytogenetics is no longer necessary.

Researchers are looking at genetic rearrangements used to monitor for residual disease in lymphomas and at *Her-2/neu* gene amplification in breast and ovarian cancers to determine tumor aggressiveness. Lastly, the series of chromosomal alterations that have been associated with the progression of colorectal tumors from benign adenomatous polyps to frank carcinomas has received great attention as an exciting new diagnostic indicator.

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Scientists Find Better Ways to Find Better Drugs

By Kara Smigel

The National Cancer Act of 1971 called for the "aggressive pursuit" of the development of new and better anti-cancer drugs. In the next 20 years, the National Cancer Institute tested more than 150,000 new compounds, selected about 150 for human trials, and helped almost 30 new anti-cancer drugs reach the marketplace.

The discovery of new drugs usually happens in one of four ways, three of which led to marketed drugs in the last 20 years. For example:

- Cisplatin, a drug useful in treating several types of cancer, was found serendipitously;
- The discoveries of streptozotocin and mitoxantrone resulted from mass screening of new compounds with previously unknown antitumor activity;
- Carboplatin, lomustine, and carmustine were initially prepared as structural relatives or analogues of previously known anti-cancer drugs;
- The fourth route of drug discovery, rational synthesis, is gaining importance as an area of research, although no recently marketed drugs have resulted.

The empirical mass screening of potential anti-cancer drugs is a labor-intensive and expensive job for which the government has traditionally taken the major responsibility.

Pharmaceutical companies, universities, other government agencies, as well as international researchers often turn over to NCI their hopeful compounds for preclinical screening and/or development. Thus, the vast majority of approved anti-neoplastic drugs in the United States were developed, in some way, by NCI.

Low Return

"On the scale that we screen potential anti-cancer drugs, it is a high-risk, low-return kind of project," explained Saul Schepartz, Ph.D., who headed the preclinical drug research and development program at NCI in the early 1970s, and works with the Developmental Therapeutics Program today.

Created in 1955, the Cancer Chemotherapy National Service Center became part of the institute's overall cancer chemotherapy program in 1965. In 1972, the program expanded as a result of the National Cancer Act and became a formal part of NCI's Division of Cancer Treatment.

By then, the hallmark of the existing program was a series of steps and decision points used to guide preclinical drug development. The "linear array" guided potential anti-cancer drugs through rigorous testing, beginning with laboratory studies and ending in large-scale human trials. (see News, *J Natl Cancer Inst*, May 15, 1991.) Various checkpoints along the way assessed the worth of each drug.

The rigorous standards within the array invariably weeded out the majority of compounds tested. In the early 1970s, NCI received as many as 30,000 new compounds yearly and screened about 10,000. Of these, typically about 200 showed some anti-cancer activity and perhaps eight reached human trials. The ratio of

new compounds tested to drugs that reach clinical research remains about the same today.

After the Act

After the National Cancer Act, the absolute number of compounds submitted to the institute increased for a while, but the ultimate number of drugs that reached the market did not increase substantially, said Schepartz.

In 1975, NCI's initial drug screen was changed to the more sensitive of the two mouse leukemias that had been the initial screen for years.

For the next 10 years, the P388 leukemia mice were used almost exclusively for the primary screen for all new compounds submitted to NCI. The secondary screens included nude (athymic) mice implanted with human tumors.

"There was a feeling that human tumors would be more predictive," said Schepartz. "And the development of the nude mouse xenograft allowed human tumors to be used for secondary screening."

Researchers were increasingly concerned that a primary screen that found drugs to treat leukemia might not be the best way to screen drugs for other cancers. In 1985, in order to change the primary screen to a battery of in vitro assays employing a diverse disease-oriented panel of human tumor cell lines, NCI had to slow and eventually stop the mass screening of potential drugs using the older system.

For the more than 4 years during which the new screen was being established there was an essentially complete cessation of screening of new compounds. In spite of this major interruption, "there was enough historical perspective to convince people that the change was due," explained Michael R. Boyd, M.D., Ph.D., head of NCI's Laboratory of Drug Discovery, Research, and Development.

20,000 Screened

Currently, about 20,000 samples are being screened each year (see *J Natl Cancer Inst*, July 4, 1990, and June 5, 1991). Half of these are pure compounds submitted by outside sources such as drug companies and university researchers. The other half come from internal NCI researchers or are extracts from natural products gathered under contract from around the world.

Since 1986, NCI has contracted with botanists and other scientists to collect additional natural products to test in the new human tumor cell line screen. While collecting the

FDA Approved Drugs

Cytoxic anti-cancer drugs approved for marketing in the U.S. since 1972 are listed below.

Development of some of these drugs took place before the National Cancer Act, although Food and Drug Administration approval for marketing was after 1971.

Synthetic Drugs
- decarbazine
- lomustine (CCNU)
- carmustine (BCNU)
- cisplatin
- mitoxantrone
- carboplatin
- levamisole
- hexamethylmelamine
- fludarabine

Alkylating Agents
- streptozotocin
- ifosfamide

Plant Alkaloids and Antibiotics
- bleomycin
- doxorubicin
- mitomycin-C
- L-asparaginase
- daunomycin
- etoposide
- idarubicin

immense diversity of novel plants, marine organisms, and microbial products is an expensive and time-consuming venture, researchers agree that the search for new anti-cancer natural products is an important priority.

"The lull in natural product research over the last few decades, combined with the reduction in global plant biodiversity has resulted in an urgent race against time," said Michael J. Balick, Ph.D., director of the New York Botanical Garden Institute of Economic Botany and an NCI contractor collecting tropical plants.

A good example of the potential of natural products is taxol, a drug made from the bark of the Pacific yew tree, and collected for screening in the early 1960s. The drug shows great promise in treating solid tumors such as ovarian and breast cancer, and a concerted effort is under way to increase the supply of the drug.

Another beneficiary of the hunt for new natural product drugs has been a large-scale anti-HIV drug screen created by NCI in 1987. Set up parallel to the anti-cancer drug screen, thousands of synthetic compounds as well as natural products are being tested against cells infected with HIV. NCI tests and develops potential anti-HIV compounds for clinical trials through intramural NCI researchers and the National Institute of Allergy and Infectious Diseases.

Rational Drugs

On the flip side of drug discovery through screening of compounds with unknown properties, "rational" drug development may grow in importance. "Rational" drugs are designed with a specific action in mind—they are built from the ground up to fit a specific purpose.

"There is a decreasing reliance upon the NCI screens as the sole means for the determination of drug development priorities," said Boyd. Researchers are not waiting for random screening to locate compounds with anti-cancer activity—they try to conceive and create them directly instead.

J. Anthony R. Mead, Ph.D., who heads NCI's Grants and Contracts Operations Branch, agrees about the importance of extramural drug discovery. "The government can't come up with all the ideas," said Mead.

Since 1983, for example, NCI has been funding cooperative agreements with a variety of researchers at nongovernment institutions to be Cooperative Drug Discovery Groups. The groups use scientific rationales to design and synthesize new anti-cancer drugs.

"The 1990s will mark an era of continuing evolution of strategies and tactics for new anti-cancer drug discovery," Boyd predicts.

1971

NATIONAL CANCER PROGRAM

1991

Scientists Develop New Interest In Cancer Vaccine Research

By Patricia A. Newman

Cancer researchers now are studying vaccine development with renewed interest, after nearly two decades of slow progress toward an elusive goal.

The research is taking a variety of different directions. Immunologist John Sogn, Ph.D., of the National Cancer Institute, said that "there is an enormous amount more known, both about the immune response to cancer and about immunology, now than there was 20 years ago. As a result, approaches have changed dramatically."

Easy Problems Solved

Twenty years ago, vaccines were worked out empirically, using the methodology then available. Said Sogn, "In the 1970s, relatively little progress was made in vaccines in either the conventional anti-viral sense or in vaccines against cancer. What happened was that all the easy problems had been dealt with."

During the 1970s, the advent of monoclonal antibody technology made possible the dissection of cells, viruses, and antibodies, resulting in a better understanding of the components of the immune system. That knowledge, and the emergence of recombinant DNA technology, resulted in new approaches to vaccines.

Dr. Edward Tabor

Because cancer is more than 100 distinct diseases, "the term cancer vaccine generally makes scientists cringe, " said Edward Tabor, M.D., NCI's associate director for biological carcinogenesis.

"You can't just call a scientist and say, 'tell me about cancer vaccines,' because some of them are really dealing with cancer antigens, and just the term cancer vaccines is almost an oversimplification."

Since 1971, two cancer virus vaccines have been approved for marketing, one against the human hepatitis B virus and one against the feline leukemia virus.

Neither Known

Neither these viruses nor their associations with the cancers were known in 1971. "The feline leukemia virus was actually discovered a little before 1971, but certainly its link to naturally occurring cat leukemia had not been made prior to 1971, and the hepatitis B virus had not been identified," said Max Essex, D.V.M., Ph.D., of Harvard University.

The first human hepatitis B vaccine was licensed for use in the United States in 1981 and became commercially available in 1982. In 1984, a recombinant vaccine became available. It was the first human vaccine made with molecular biological techniques.

Cost Causes Cancer

"Worldwide, cost is a big problem," said NCI's Tabor. Adds Essex, "Cost is keeping the vaccine from being used in parts of Asia and Africa where it might do the most good."

However, more than 20 developing countries already have universal infant immunization programs to protect against HBV. Consequently, scientists will be watching populous parts of the world, such as China, to see if immunization also protects against liver cancer. In endemic areas, liver cancer begins to appear between ages 20 and 40, and it will be years before scientists know whether the vaccine works against cancer.

HBV vaccination is not expected to eliminate liver cancer entirely, Some liver cancers are virus negative, and the impact of other factors, such as aflatoxin exposures and other viruses, such as hepatitis C virus, is unknown. In addition, said Tabor, "It is now becoming apparent that there are some variants of the hepatitis B virus that are particularly virulent and that, at least theoretically, might not be protected against by the vaccine."

Essex predicts, "If you looked 30 years later at [vaccinated populations], the rate of liver cancer might be reduced 80%."

A less likely vaccine prospect is the human T-cell leukemia virus. Discovered in 1978, the virus is endemic in certain parts of Japan and the Caribbean and has become increasingly important in the United States.

"It's very clear that we could mount a program against HTLV-I that could work without great difficulty, but because the cancer it causes is rare, it wouldn't necessarily be cost-effective," said Essex. "We could learn a lot from it, however, and certainly save some lives."

HPV Vaccine Prospect

Cancer of the uterine cervix, associated with papillomavirus, is a major cause of death worldwide, and a safe and effective vaccine would have a major impact. Papillomaviruses are now suspect in several cancers, primarily those affecting the genital tract in both sexes.

Dr. Max Essex

"Unfortunately," said Essex, "we're a little farther behind" in understanding the immune response to the human papillomaviruses than with HBV. It is known, for example, that the *E6* and *E7* genes of HPV and their "oncoprotein" products are expressed in cervical cancer cells. These oncoproteins inactivate the effects of normally occurring tumor suppressor proteins and are potential unique targets for a vaccine.

However, scientists do not yet understand the immune system's responses to viral infection, nor how to elicit an effective systemic immune response that also elicits immunity in mucosal tissue.

EBV Vaccine

The Epstein-Barr virus is firmly established as a causal agent in nasopharyngeal cancer and certain lymphomas in endemic areas of Africa and Asia. It is the cause of infectious mononucleosis in the United States, where it is also suspected of playing a role in AIDS-related lymphomas.

"There's no doubt in my mind that a vaccine could be made against Epstein-Barr virus to prevent infection so that nasopharyngeal cancer, Burkitt's lymphoma, and even infectious mononucleosis could be prevented," said Essex.

However, more research is needed, "not as much as for papillomavirus, but more than for HTLV-I." A high molecular weight envelope glycoprotein, gp340, has evoked some protective immunity in marmosets, and limited studies are under way to see if it is antigenic in people.

AIDS vaccine research is likely to reap large dividends for cancer vaccines, according to researchers. AIDS patients produce antibody to

Dr. Peter Nara

the HIV virus, but questions about whether it is protective persist. According to Peter Nara, D.V.M., Ph.D. of the NCI-Frederick (Md.) Cancer Research and Development Center, HIV generates tremendous amounts of cell-free virus soon after infection. This is followed by a period of abatement.

Virus Escapes

During this time, HIV mutates in sites distant from the region that elicits an immune response. Those changes affect the shape of the envelope, allowing the virus to escape the immune system. Later on, said Nara, "the virus has amino acid substitutions occurring inside the antibody binding site." This changes the structure again, disturbing antibody interaction.

Nara believes the immune system makes antibody during the initial infection of the dominant strain of HIV. "The virus is very smart. It hasn't changed its immunodominant epitope. It changes its shape a little bit so antibody can't bind very well. But the part that is initiating the B-cell response is the same." the body is making antibody, but to a virus that is already gone.

Identifying and understanding how conformational epitopes are preserved, Nara thinks, may be important for cancer vaccines as well. "The humoral immune system generally recognizes molecules based on shape. You can have a shape made up of lots of amino acid sequences, based on how they're folded. You could have 100 different sequences, but when assembled in the native conformation, they'll give you only maybe 10 shapes. That's important to know."

Need Understanding

Unfortunately, scientists do not yet understand how higher-ordered protein structures fold. To find cross-protective antibody against HIV, Nara would like to know first, the naturally occurring families of antigens of the virus, and second, the crystallographic structure of the conformational epitope. "We're very bad currently at identifying and then mimicking these conformational epitopes using recombinant DNA technology."

Essex believes HIV vaccine research will teach scientists how to build a better cancer vaccine. Understanding the cytolytic T cell responses to different parts of the HIV envelope, he said, will show scientists how to splice together an antibody and delivery system to program a specific immune response.

Strategies for the rational design of cancer vaccines today include efforts not only to prevent infection by certain viruses, but also to prevent recurrences and to treat patients with cancers that are not necessarily viral in origin. A large number of studies are directed toward stimulating anti-tumor responses via the T lymphocytes.

These approaches have often relied on the identification of antigens specific for a particular cancer. "There had been hopes in the late 1960s and early 1970s, with the demonstration that many rodent tumors had tumor-associated transplantation antigens, that immunization would be an effective approach," said Ronald Herberman, M.D., director of the Pittsburgh Cancer Institute, at the 1991 meeting of the American Association for Cancer Research.

"However, in the later 1970s and particularly the early 1980s, this whole approach of specific immunotherapy fell into disrepute or evoked a great deal of skepticism."

Tide Turning

However, the tide has turned. Herberman said at AACR, "Probably the reason is there have been a few groups who persisted and have done both good preclinical studies or even clinical studies with active immunotherapy and have demonstrated that in a number of situations this

approach continues to hold promise."

For example, Olivera Finn, Ph.D., also at PCI, is looking at ways to use immune system reactivity to protein molecules called mucins to kill cancer cells. The mucin molecules secreted by cancer cells stimulate T cells. Using synthetic mucin in a plasmid vector, Finn hopes to generate both T and B cell immune responses against cancer cells.

Novel Approaches

One novel approach about to enter clinical testing, using recombinant vaccinia virus, is enhancing the expression of genes and potentially immunogenic tumor-associated antigens.

Another approach has been to enhance the immune response to cancer by upregulating the expression of major histocompatibility complex antigens on the cancer cell surface. Cytokines such as tumor necrosis factor, interferon, and interleukins increase the expression of these antigens and also directly enhance the invasion of the tumor by T cells.

Monoclonal antibody and recombinant DNA technology have enabled scientists to pin down specific parts of the immune system which respond to a test vaccine, and which do not. "When you can distinguish levels of failure," said NCI's Sogn, "you can design strategies to get around them."

In the past 10 years, the emphasis has been on "the search for components of tumor cells that could mediate rejection by T cells rather than looking for tumor-specific molecules that could generate antibody responses," Sogn said. "The bottom line on everything that has been learned to date about the immune system is that the response to cancer, for it to be effective, has to begin at the level of T cells."

1971-1991: Virus Cancer Research Pays Rich Dividends

By Elaine Blume

Dr. John Moloney

When he is asked what cancer virology accomplished during the past 20 years, John Moloney, Ph.D., director of the National Cancer Institute's virology program in the 1970s, answers, "We know what causes cancer. The viral oncology program led us to discover oncogenes in cells."

Researchers in 1971 were debating the merits of three closely related hypotheses that purported to explain how cancer developed. The provirus, oncogene, and protovirus theories all asserted that animal cells contained genetic information from tumor viruses. Certain events, according to these theories, could activate this information, and cancer would be the result.

The discovery of reverse transcriptase in 1970 added to the credibility of these hypotheses. This unique viral enzyme makes DNA copies of viral RNA. It was discovered by Howard M. Temin, Ph.D., (who had predicted its existence) and his co-workers at the University of Wisconsin and, independently, by David Baltimore, Ph.D., then of the Massachusetts Institute of Technology. The existence of the enzyme provided a plausible mechanism by which cancer-causing information from RNA viruses could be transferred to and integrated into the DNA of the cellular genome, permanently transforming a cell.

Hunting for a Virus

In 1971, scientists were also racing at full tilt to isolate a human tumor virus. The National Cancer Institute's Special Virus Cancer Program, had laid the groundwork for this search, which had so far produced many rumors and false leads, but no bona fide human tumor virus.

"In 1964, NCI's director, Kenneth Endicott [Kenneth M. Endicott, M.D.], went to Congress and got $10 million to create what became the Virus Cancer Program," Moloney recalled. "That was the beginning of an organized effort to determine whether viruses cause human cancer, and if they did, what we could do about it. But it was a terribly long fight to get the Virus Cancer Program at NCI. It was very difficult."

Alan S. Rabson, M.D., director of NCI's Division of Cancer Biology, Diagnosis, and

Centers, agreed. "Dr. Endicott deserves great credit for setting up the Virus Cancer Program," Rabson said. "Congress deserves great credit, too, for providing the financial support for the program.

"At the time, there was a lot of opposition. Many scientists said we shouldn't promise what we might not be able to deliver. But Endicott was somehow able intuitively to see how important this type of research could be. And indeed, this program supported the discovery of reverse transcriptase and led to a whole new understanding of the etiology of cancer."

In the early 1970s, J. Michael Bishop, M.D., and Harold S. Varmus, M.D., with their co-workers at the University of California at San Francisco, undertook to test the oncogene theory of NCI's Robert J. Huebner, M.D., and George J. Todaro, M.D. This theory held that cancer-causing genes of RNA tumor viruses (called "retroviruses" after reverse transcriptase was discovered) were part of the genetic baggage of all vertebrate cells.

Bishop and Varmus therefore set out to find *src*, a known viral oncogene, in the DNA of animal cells. The researchers set off scientific shock waves when, within a few years, they discovered copies of the gene in healthy chickens, in other birds, in fish, and also in mammals, including humans. Bishop and Varmus received a Nobel Prize for this work.

Oncogenes

At first, scientists believed that the new results confirmed the oncogene theory. But as they became better acquainted with viral oncogenes and with the cellular counterparts of these genes, they concluded that both the oncogene theory and the related provirus and protovirus theories were only partially correct.

These hypotheses had all incorporated the central truth that the genetic instructions for cancer were permanently present in cells, though usually in a latent or controlled state. The theories were also correct in affirming that this potentially treacherous genetic information was related to that found in RNA tumor viruses.

What nobody had guessed was that the cancer-causing genes were normal—in fact, essential—cellular genes that only caused problems when they or their control systems were altered. And, the resemblance between cellular and viral oncogenes, scientists eventually agreed, had not arisen because animal cells had incorporated viral genes. Rather, the reverse was true. Certain viruses, in the course of evolution, had acquired key genes with deadly potential from their cellular hosts.

Laid Groundwork

"All of this work at the molecular level was developed through the efforts of the Virus Cancer Program," Moloney noted. "If you talk with some of the young men today, they feel that we laid the groundwork. We oriented people toward the genetic approach, which is what they do now—truly molecular level work, which is really beautiful work and terribly exciting.

"[NCI's virology program] contributed the initial information that makes it possible now for individuals to go on and further identify viruses as causes of human cancer. It was a wonderful, interesting, and rewarding effort."

After several false starts, the search for human tumor viruses finally bore fruit in 1980, when Robert C. Gallo, M.D., and his colleagues at NCI identified a retrovirus as the cause of human T-cell leukemia. At about the same time, Japanese scientists had independently been studying a disease known as adult T-cell leukemia, which was endemic in parts of Japan. A virus isolated from cells of patients with this disease later turned out to be identical to Gallo's virus, HTLV-I.

"The original idea behind the search for a human leukemia virus," Rabson said, "was the belief that if, as had already been shown, leukemia in chickens could be caused by a virus, and leukemia in mice could be caused by a virus, there was absolutely no reason why leukemia in humans could not be caused by a virus. And that turned out to be true, although

viruses don't appear to be responsible for most human leukemias."

HIV

Today, a new retrovirus, human immunodeficiency virus, or HIV, has moved to center stage. "If AIDS had come on the scene in 1971," Rabson said, "we would have been completely baffled. But a decade later, when AIDS did appear, the wonderful groundwork laid by the cancer virus program made it possible for HIV to be isolated and identified relatively quickly and for a useful blood test to be rapidly developed."

HIV does not appear to be a tumor virus in the usual sense. But it is certainly associated with several cancers, especially Kaposi's sarcoma and non-Hodgkin's lymphoma, though just how it helps to produce these tumors remains unclear.

DNA-containing viruses can also trigger cancer. In the early 1930s, Richard Shope, M.D., and F. Peyton Rous, M.D., of the Rockefeller Institute, found that a filterable agent in an extract of warts (a form of benign tumor) from wild rabbits could induce warts in other wild rabbits and carcinomas of the skin in domestic rabbits. Later, the agent was found to contain DNA and was named the Shope papillomavirus. Subsequently, several other groups of DNA viruses have been shown to induce tumors in particular animal species, including humans.

"The evidence is compelling that specific viruses are associated with specific human cancers," said Peter M. Howley, M.D., chief of NCI's Laboratory of Tumor Virus Biology.

Hepatitis B Virus

A striking example of such an association is that between hepatitis B virus and liver cancer. Although primary liver cancer is relatively uncommon in the United States, it is the most common form of cancer in China, some parts of Asia, and Africa. Each year, it is responsible for hundreds of thousands of deaths worldwide.

In 1981, R. Palmer Beasley, M.D., and his associates at the University of Washington demonstrated that individuals with chronic hepatitis B virus infection were far more likely than others to develop liver cancer.

Most people infected with HBV recover completely. But infants infected during the first months of life are very likely to become chronic carriers. And transmission of HBV from mother to infant at birth is one of the most common ways that the virus spreads in Asia and in some parts of Africa.

An excellent second-generation vaccine against HBV, produced with recombinant DNA technology, is now available and is being used to inoculate infants in many developing countries (see News, *J Natl Cancer Inst.,* Oct. 16, 1991). But in order to break the cycle that begins with infection at birth, universal vaccination may need to be carried out for at least two generations. Unfortunately, cost is restricting use of the vaccine.

In spite of these limitations, vaccination against HBV promises to drastically reduce the worldwide toll from liver cancer in coming decades.

EBV and HPV

Other DNA viruses also cause many cases of cancer around the world. A large number of Chinese, for example, are afflicted with nasopharyngeal carcinoma, and African children may suffer from Burkitt's lymphoma. Epstein-Barr virus, best known in the United States as the cause of infectious mononucleosis, clearly plays a role in both of these cancers, though it is clear that other factors are important, too.

Cervical cancer also appears to be triggered by a virus. Years ago, the distinctive incidence pattern of this cancer led scientists to suspect that a transmissible agent might be involved. They observed, for example, that women who became sexually active at an early age or who had multiple sexual partners were at increased risk.

For a time, type 2 herpes simplex virus was the chief suspect. More recently, though,

researchers have shown that certain "high-risk" types of human papillomavirus are key players in cervical cancer. DNA from these viruses is found integrated into the genomes of the cancer cells.

Evidence of HSV-2 infection is now viewed as simply a marker for sexual activity. This virus does not seem to play a direct role in causing the cancer.

Diane Solomon, M.D., of NCI's Laboratory of Pathology points out, though, that infection with even a high-risk type of HPV is not sufficient to cause cervical cancer. "Only a small percentage of women infected with high-risk HPV will go on to develop premalignant changes," Solomon said. "Obviously, other factors must also play a role."

Multiple Steps

After proto-oncogenes (the "normal," unaltered form of cellular oncogenes) were found in healthy cells, researchers began studying the association of cancers with the loss of specific genes. Eventually, it became clear that progression to cancer typically requires multiple steps, some involving abnormal activation of growth-promoting genes (oncogenes) and others taking the form of loss or inactivation of genes (tumor suppressors) that normally hold cell growth in check.

At least some viruses that induce cancer do so by interacting with the products of tumor suppressor genes. For example, the E7 protein of HPV types associated with cervical cancer binds to and inactivates the tumor suppressor protein RB, while a second protein, E6, from the same viruses complexes with another key tumor suppressor protein, p53. The latter complex, though, doesn't merely take p53 out of the active arena. NCI's Howley and Princeton's Arnold J. Levine, Ph.D., along with their co-

Dr. Arnold J. Levine

workers, have shown that formation of the complex actually triggers degradation of the p53 protein.

Oncogenic proteins of other DNA tumor viruses have also been shown to interact with tumor suppressor proteins, especially RB. These findings have added to the body of evidence indicating that all cancer ultimately results from abnormal activation of oncogenes or their products, or from loss or inactivation of tumor suppressor genes or proteins.

"NCI's tumor virus program was a targeted program that worked out wonderfully well," Rabson said. "The program showed that, even when you target money, if you give it to good scientists, they will figure out how to use it in effective ways. In this case, the taxpayers got a great return on their investment."

Biotech Industry Flourishes With Cancer Research Advances

By Cori Vanchieri

The cash infusions provided to the National Cancer Program by the 1971 National Cancer Act fueled scientific discoveries that have dramatically advanced understanding of the cancer process. With a vision of how these discoveries could affect cancer diagnosis and treatment, a whole new industry was born, designed to take basic research and make it useful to cancer patients.

Taking their lead from developments in science, U.S. commercial biotechnology firms have brought to market monoclonal antibodies, colony-stimulating factors, and other biologicals. According to industry observers, the future never looked so good.

Dr. Ashley Stevens

"In the early 1980s, the certainty wasn't there that it was for real. It was a rollercoaster ride," said Ashley Stevens, Ph.D., director of the Office of Technology Transfer at the Dana-Farber Cancer Institute, Boston. "Now, there is no doubt in people's minds that biotech will produce blockbuster drugs."

Stock Sales

This confidence has been reflected in the stock market. "More [money] was raised in the last year than has ever been seen before," he added. "Even small companies with preclinical drugs can get money." During 1991, biotech companies sold $17.7 billion in stocks, the highest 5-month total in history.

Today, 750 biotechnology firms have about 100 drugs in various stages of development; more than half of those drugs target cancer or cancer-related conditions. Many products that have been in research for years are now becoming commercial.

Industry revenues for 1990 were estimated at $2 billion, according to the U.S. Office of Technology Assessment. Sales are expected to reach $15 billion by the year 2000, according to Mark D. Dibner, Ph.D., of the North Carolina Biotechnology Center.

Science and Policy

The industry got started by people moving from academia to the commercial sector, or working in both, according to Stevens. The first biotech firm, Genentech, South San Francisco, was founded in 1976 by venture capitalist Robert Swanson with Herbert Boyer, Ph.D. Boyer,

while at the University of California, San Francisco, created the first recombinant DNA with Stanley Cohen, M.D., of Stanford University.

But just as important as the scientific discoveries were the federal policies that were put in place in the early 1980s to make the investments financially worthwhile, such as capital gains incentives and patent protections, Stevens said.

For example, the capital gains tax cut of 1978 caused an enormous influx of funds to venture capital, Stevens said. In addition, the Bayh-Dole Act of 1980 gave universities the means and the incentives to aggressively market their technology, and in 1981 the Chakrabarty patent decision established the patentability of genetically altered living organisms.

In 1982, the establishment of the U.S. District Court of Appeals for the federal circuit swung the balance from patents being easily violated to providing a reasonable degree of protection.

Still, according to a survey by the North Carolina Biotechnology Center, biotech firms view the Food and Drug Administration regulatory process and the U.S. patent process as the top barriers to the success of their companies. A recent General Accounting Office report found the average patent for a genetically engineered product took 4 years to process.

To the Marketplace

Once approval comes through, long-awaited drugs move quickly into the marketplace. Upon receiving FDA approval in February 1991 for Neupogen, its granulocyte-colony stimulating factor, Amgen shipped $53 million of the drug during the first month after approval.

Since then, more than 35,000 patients have received the drug, according to George Morstyn, M.D., Ph.D., vice president for medical and clinical affairs. Neupogen is now approved for use in more than 20 countries. The Thousand Oaks, Calif., company began clinical trials of the drug in 1986.

Wall Street Records

Stock market interest in biotech firms was strong in the early 1980s. Genentech's initial public offering in 1980 set a Wall Street record for the fastest price-per-share increase—$35 to $89 in 20 minutes. Then in 1981, Cetus set a Wall Street record for the largest amount of money raised in an initial public offering—$115 million.

The first 9 months of 1991 saw a 24% increase in biotech stocks. Even the conservative Boston University has invested one-third of its endowment in the Massachusetts-based biotech firm, Seragen.

"[The biotech industry] is peculiarly an American industry that is predominantly an outgrowth of NIH-supported research," said James B. Wyngaarden, M.D. "It's an industry we don't want to lose."

Wyngaarden, former NIH director, chaired a working group on biotechnology under Vice President Dan Quayle's Council on Competitiveness. Wyngaarden said the vice president is concerned about the health of the biotech industry and wants to make sure that it doesn't go the way of computer chips and consumer electronics.

The National Cancer Institute established an Office of Technology Development in November 1987 to oversee implementation of legislation, rules, and regulations relating to Cooperative Research and Development Agreements (CRADAs), patents, licenses, and royalty income.

"NCI has a long history of developing cancer drugs with industry," said Thomas Mays, Ph.D., J.D., director of the office. "NCI's program is one of the most extensive in the government." In fiscal year 1991, approximately 24 NCI CRADAs were active, another 18 pending. And 2,200 contracts were drawn for exchanges of biologic materials between NCI researchers and industry.

A sign of things to come, according to industry analysts, is the recent acquisition of Genentech, Inc., by Swiss pharmaceutical giant

Hoffmann-LaRoche, Inc. A recent survey showed that three of four chief executives of closely held biotech firms expect future funding to lie in acquisitions from other firms rather than in the public market.

Stability

The merger has provided stability for Genentech, now that Roche owns 60% of the biotech firm and only 40% is traded on the New York Stock Exchange. The company can count on putting 40% of its resources into R&D, according to its public relations director, Jack Murphy.

Hoffmann-LaRoche bought an interest in Genentech in order to have a long-term strategic investment in a key industry that has already influenced the pharmaceutical sector, according to Jürgen Drews, M.D., president of international pharmaceutical research and development for Roche. "We can expect that the impact that has just started will be much more massive in the coming years."

Industry collaborations with academia are becoming more commonplace as well. Pharmaceutical firms are making large investments in cancer research institutions, hoping to reap the benefits in product development and marketing (see News, *J Natl Cancer Inst,* Nov. 6, 1991). Dana-Farber's Stevens explained that its collaboration with Sandoz, for example, brings together the strengths of both parties.

"It allows our scientists to apply state-of-the-art immunology and molecular biology to develop ways of finding new drugs. But we're not good at screening hundreds of thousands of compounds—industry is," Stevens said.

"A true partnership has evolved between American industry and academia over the last 10 years," he said. "It works for the good of American industry and the future of health care."

Industry Appealing

John Holcenberg, M.D., vice president and director of clinical affairs at Immunex, Seattle, explained why he moved from academia to

Dr. John Holcenberg

industry. "If I wanted to clone a gene in my old lab, I would have two to three staff members working on it and it may take 6 months. Here, we have enough people to do the job in 1 month."

He described the advantage of having a whole group in one facility to direct itself at one project. The close interaction between basic scientists and clinical scientists also proves useful, he said.

And the interaction goes beyond the walls of Immunex. Like many other biotech firms, this company collaborates with 30 different institutions throughout the United States and abroad, as well as with other pharmaceutical and biotech firms, like Syntex in Palo Alto, Calif.

Immunex received FDA approval in March for Leukine, its protein that fights infections in cancer patients undergoing bone marrow transplants.

Its latest drug, called PIXY321, is in phase I studies. This drug is a combined molecule of GM-CSF and interleukin-3. Immunex expects it to prove useful in allowing granulocytes as well as platelets to recover from chemotherapy. Until now, platelets have been a problem, Holcenberg said. By combining drugs, as attempted with PIXY321, past toxicities can be avoided.

"In the next 10 years, the biotech firms will figure out how to make cells increase or decrease in numbers and activity," he said. "It will revolutionize the way we treat patients."

"We have succeeded in upgrading the tool chest that scientists have to understand the can-

cer process," said Howard Jaffe, M.D., director of clinical research at Genentech. "The jury is still out in terms of whether or not these new tools will lead to survival benefit in the short term. They certainly will in the long term."

"We see our role as putting in place the technologies that can translate [scientific discoveries] into clinical practice," Morstyn said. "We can offer researchers the ability to turn their discoveries into clinically useful products."

Science Will Lead

In years to come, "look at developments in science; they will lead industry," he said. The next challenge is to correct diseases using various genetic approaches. At least 13 companies and 33 organizations are studying oncogenes. Jaffe added that along with oncogenes, many companies are looking at manipulating DNA/RNA levels with DNA blocking and antisense oligonucleotide technologies, while others are considering gene therapies.

For example, Genentech has begun phase I trials with murine monoclonal antibodies directed against the gene product of the *Her-2/neu* oncogene, according to Jaffe. The company is working with the University of California at Los Angeles and NCI and plans to work with Georgetown University, Washington, D.C., and Memorial Sloan-Kettering Cancer Center, New York.

And biotech is more than drugs, according to North Carolina's Dibner. He is seeing more activity in using biotechnology to detect toxins in the environment as well as clean up the environment, which could ultimately reduce environmentally related cancers.

"Ten years ago, most wouldn't believe that what's been achieved could have [been]," Morstyn said. "And there is so much new to be developed."

Of Pedigrees, Probes, and p53: 20 Years of Family Studies

By Nancy Volkers

When President Richard M. Nixon signed the National Cancer Act in 1971 amidst flash bulbs and microphones, he made his mark on the nation's war on cancer.

In 1988, with much less publicity, former President Jimmy Carter made his own mark by donating his chromosomes to an ongoing family study of pancreatic cancer headed by John J. Mulvihill, M.D., chairman of human genetics at the University of Pittsburgh.

Today, scientists examine families such as the Carters, looking for clues as to why cancer, like high cheekbones or curly hair, can run in the family.

High-Risk Families

Explained Joseph F. Fraumeni, Jr., M.D., associate director for the National Cancer Institute's Epidemiology and Biostatistics Program, "These families are rare, these really high-risk families. But the susceptibility is so striking that it's easy to detect an underlying defect. And this defect may exist in a more subtle form in other patients with these tumors."

Thus, a "family study" may involve families initially, but has effects that reverberate far beyond a specific group of relatives.

Dr. Joseph F. Fraumeni, Jr.

However, in 1971, "there was little interest in families and the role of genetic susceptibility to cancer," Fraumeni said.

This lack of interest stemmed from accumulating evidence that environmental factors, not genes, were critical to the development of cancer.

Geographic variation in cancer rates, as well as studies that showed an immigrant's risk drifted away from that of the country of origin and aligned with that of the new country, underplayed the genetic component.

"In all this heady excitement about the environment," Fraumeni said, "I think genetics and family studies took a back seat."

Li-Fraumeni Syndrome

Fraumeni and other researchers, though, weren't discounting heredity. In 1969 Fraumeni and Frederick P. Li, M.D., now at the Dana-Farber Cancer Institute, Boston, described a syndrome involving family members markedly susceptible to cancers including leukemia, breast cancer, and brain cancer. Radiation treatment made these patients further susceptible to soft tissue sarcomas in the areas exposed to radiation.

These observations, coupled with advances in molecular genetics, eventually led to the 1990 discovery of the mutation of the *p53* tumor sup-

pressor gene that causes Li-Fraumeni syndrome. (See News, *J Natl Cancer Inst*, Jan. 16, 1991).

"The technology wasn't such that we would have been able to find this in 1971," Fraumeni said.

The technology in 1971 relied mainly on scientists' observations. What they knew about familial cancers depended on patterns they could see in a pedigree or chromosomal aberrations obvious under a microscope.

"Back then, [genetic counselors] could tell you a lot if your problem was a classic Mendelian genetic disease. And there were a few diseases they could test, like sickle cell anemia or [phenylketonuria]," said Eric T. Juengst, Ph.D., director of the Ethical, Legal, and Social Implications Program of the National Center for Human Genome Research at the National Institutes of Health.

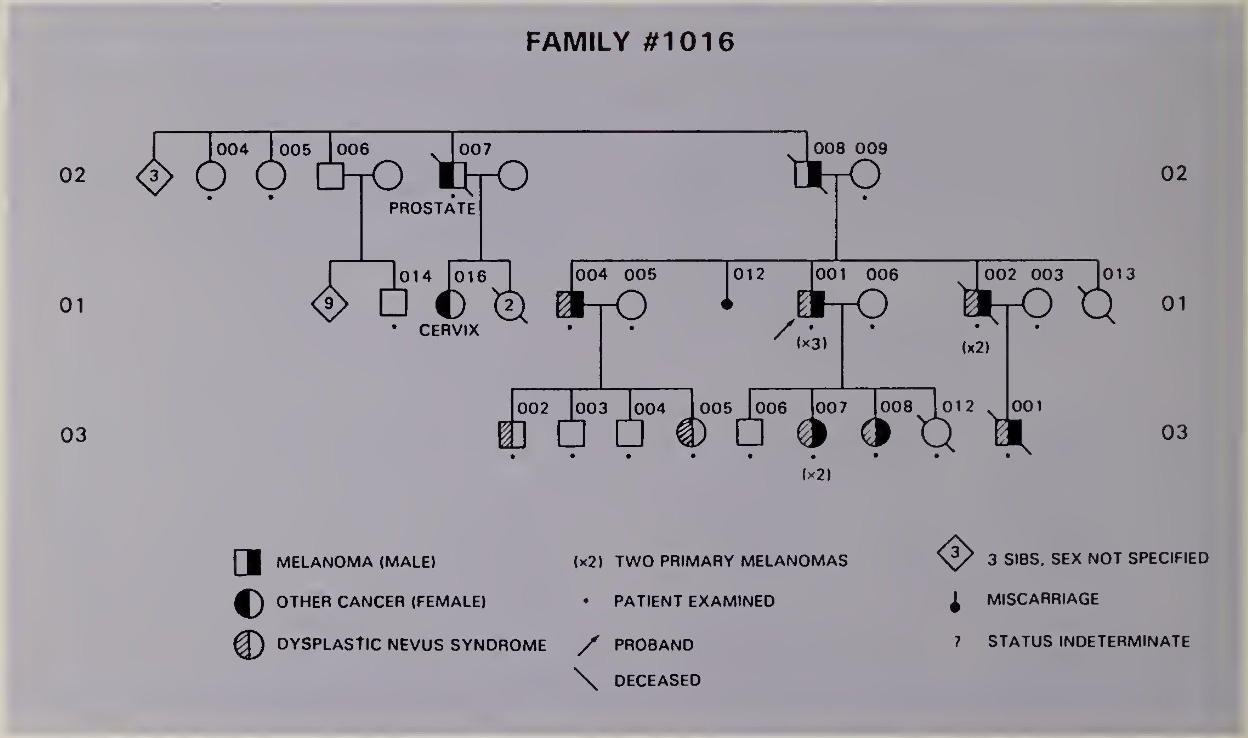
"But now," he said, "there's a much longer list of disease genes that we can test directly for. And, we now know that there are genetic markers for cancer risk."

Which Came First

Scientists' opinions differ as to which was the driving force in family studies research—clinical observations or basic science advances.

Dr. Robert W. Miller

"Clinical observations were the key for laboratory scientists," explained Robert W. Miller, M.D., chief of NCI's Clinical Epidemiology Branch. "As we made these observations, technology often had to develop to the point where experiments could be done."



The above pedigree charts the cancer history of a single family. Patterns in cancer incidence can help physicians gauge the risk of each family member.

Mulvihill sees it the other way. "Given advances in epidemiology and genetics, we could ask more focused questions on genes and environmental exposures."

In the field of family studies, both seem correct. Observations of cancer trends in families often led to developments in genetics, which allowed researchers to reach the next level of questioning. This co-evolution has taken family studies deep within the cell.

Chromosome Banding

Chromosome banding techniques, perfected in the early 1970s, allowed scientists to compare regions of a healthy person's chromosomes with those of a cancer patient. Differences previously invisible could spotlight regions where disease-causing genes reside.

In a quest to understand the differences between the inherited and non-inherited forms of retinoblastoma, scientists employed chromosome banding, which showed that somatic cells of patients with the non-heritable form contained two normal copies of chromosome 13, the chromosome associated with the inherited form of the disease.

But cancer cells in these patients were different; they were missing a region of that chromosome. More extensive studies later led to the detection of the responsible gene in that same missing region.

The discovery of restriction enzymes in the early 1970s was a turning point in family studies research. The enzymes slice DNA into fragments, which can then be separated by size using a Southern blot, a type of electrophoresis first used by E.M. Southern, Ph.D., in 1975.

Detecting Culprits

By comparing a healthy family member's DNA with a diseased member's, variations may be detected. If enough family members can be studied, researchers may find that the presence of a particular variation usually coincides with disease. They can then examine the DNA fragment causing the variation for the gene responsible for the disease.

This process of "reverse genetics" is used in family studies. Instead of beginning with a gene and trying to figure out what disease it may cause, scientists pinpoint the gene, discover its protein product, and determine what flaw in the gene is responsible for the disease.

Tremendous leaps in computing over the past 20 years have also contributed to family studies research. Analyses of inheritance patterns can pick up threads of commonality scientists might miss. And programs can analyze pages of data on genetic markers and produce a probability that the scientists have found the disease-causing gene.

Genetic Patterns

Complex diseases such as cancer, of course, may be caused by several genes, and also by environmental exposures in tandem with genetic factors. But family studies are finding patterns that often associate a specific chromosomal region with different types of cancer.

Patients with inherited retinoblastoma are also vulnerable to developing osteosarcoma. Cells from these tumors had alterations in the same region on chromosome 13 as the retinoblastoma cells.

Li-Fraumeni syndrome, which encompasses several kinds of cancer, can be traced to the p53 gene, which is found on the short arm of chromosome 17. Now, there is evidence that a predisposition to breast and ovarian cancers is associated with the long arm of the same chromosome.

Common Cancer Cause?

Discovering these familial cancer "clusters" allows for identification, and surveillance of high-risk family members. But also, said Fraumeni, "we've been able to really get at more fundamental mechanisms of cancer etiology and cancer biology.

"The attractive feature of these syndromes is that they suggest a common mechanism for different tumors, rather than a bewildering array of etiologies."

If these cancers proves to have more of a common cause than previously thought, prevention, screening, and treatment would become simpler.

Some diseases predispose patients to cancer, or are precursors to cancer. These links, previously invisible, surfaced through family studies.

Melanoma is the most serious form of skin cancer; it spreads quickly, dimming chances for survival. But if it is diagnosed early, it is highly curable.

In 1974 a family study in NCI's Epidemiology Branch revealed dysplastic nevus syndrome as a precursor to familial melanoma. According to Margaret A. Tucker, M.D., chief of NCI's Family Studies Section in the Epidemiology and Biostatistics Program, dysplastic nevi are "a major precursor" in people with a family history of melanoma and an indicator of increased risk in other people with dysplastic nevi who are not in melanoma-prone families.

Familial Breakthroughs

No one had noticed the connection between the lesions and melanoma before, because no one had examined an entire family at the same time before. Now, the lesions are also implicated in nonfamilial melanoma as well. Due to these studies, doctors know to look for these lesions and, when necessary, remove them before they prove life threatening.

Family studies also led to the discovery that sufferers of familial polyposis of the colon eventually develop colon cancer. Now, when a patient is diagnosed with the condition, in which the colon is carpeted with hundreds of tiny polyps, development of cancer can be prevented by prophylactic colectomy.

The eyes of children who have lost a gene due to a deletion in the short arm of chromosome 11 lack irises; this obvious warning sign leads to early diagnosis and treatment of Wilms' tumor.

People with xeroderma pigmentosum have a DNA repair defect that leaves them vulnerable to skin cancer. Family studies exposed this predisposition and allowed for prevention and treatment.


Dr. John J. Mulvihill

Not 100% Success

Studying families with a history of cancer or a cancer-related disease does not always produce breakthroughs. Mulvihill's study on familial pancreatic cancer has produced little. Pancreatic cancer is a swift killer, and patients often die before families can be fully examined.

"We're back in the 1970s" in this study, Mulvihill said. "We just have a few hypotheses, and we'll pursue them the best we can."

But, he said, the field of family studies "has come a long way. We are . . . on a route to understanding the origins of complex cancers."

Cancer Program Becomes Case Study in Public Policy Formation

By Lou Fintor

In calling the National Cancer Act of 1971 a "Christmas gift to the nation," then-President Richard M. Nixon signed a document into law on December 23 that would, for the first time in history, make the battle against a dread disease both a national priority and a unique public policy that continues to influence the U.S. research agenda.

A variety of often opposing political, social, and scientific forces converged to produce this blueprint that declared war on cancer.

Mary Lasker

National Priority

The person most credited with bringing the Act to fruition, legendary philanthropist Mary Lasker, could not have succeeded without influential allies, including former President Lyndon B. Johnson, the Rockefeller family, Nixon confidant Elmer Bobst, and others.

It is Lasker who created and perfected what was termed "the cancer mafia," and in the process, successfully mobilized a new advocacy movement: grassroots health policy lobbying. Her foresight provided the impetus for today's myriad health advocacy groups.

Lane Adams, executive vice president of the American Cancer Society in 1971, said it took an intensive and concerted effort of researchers, physicians, and lay people to get the Act passed.

"This Act was the most significant thing that happened in cancer research and we did a lot of preaching to get it passed, using resources, contacts in Washington, and distinguished researchers," Adams said.

The National Cancer Institute had been charged since its founding in 1937 with research on the etiology and potential cure of cancer.

The National Cancer Act of 1971 made conquering cancer the national goal of a magnitude that has been compared to launching the U.S. space program and developing the atomic bomb.

Specifically, the Act provided that NCI undertake a broad-based approach "relating to the cause, prevention, and methods of diagnosis and treatment of cancer." And it added responsibilities for cancer control.

In accomplishing this mission, the political establishment provided NCI with unprecedented support:

• The biological warfare research facilities at Fort Detrick, Md., were turned over to NCI for use in cancer research.

• The director of NCI would be subject to direct presidential appointment.

• A provision allowed NCI to submit annual "bypass budget" requests directly to the president—thus avoiding layers of Public Health Service and Department of Health, Education, and Welfare (later restructured as the Department of Health and Human Services) bureaucracy.

• Other provisions created a President's Cancer Panel, which reports directly to the White House, and a National Cancer Advisory Board. Both are composed of presidential appointees.

Under Siege

These actions, which took cancer research from the scientific arena to the political realm, would set the stage for great research advances as well as bitter frustrations.

Dr. Frank J. Rauscher, Jr.

The Act was "historic in that it committed the resources of this nation to the prevention, early detection, and treatment of cancer," said Frank J. Rauscher, Jr., Ph.D., who was appointed to lead the National Cancer Program in 1972 and continued to serve through the administration of President Gerald Ford.

Yet, the war on cancer was almost immediately controversial, and continues today to attract critics.

Critics complained in 1972 that other biomedical research would suffer at the expense of cancer; that scientific knowledge was too limited to warrant such a program that they claimed promised more than it could deliver; and that research dollars would be frittered away on control activities.

Accountability

More recently, critics complained that too much emphasis has been placed on treatment and cure at the expense of screening and prevention; that too little research is successfully disseminated to clinical practice; and that the National Cancer Program has not been subjected to sufficient accountability for the more than $20 billion appropriated from fiscal 1972 through 1992.

Many believe that those who pushed the hardest for a National Cancer Program are to blame for raising public expectations too high—in a sense, setting the cancer program up for a fall.

In the period leading up to the Act, the grassroots Citizen's Committee for the Conquest of Cancer challenged the President with a petition drive claiming "MR. NIXON: YOU CAN CURE CANCER." And politicians proclaimed that curing cancer by 1976 would be "an appropriate commendation of the 200th anniversary of the independence of our country."

Rauscher said that, "Although many thought that if we can send a man to the moon, it would be nice to give the nation a birthday present in curing cancer by 1976, that belief really wasn't as firm in the scientific community."

He added that "We had an established base of scientific knowledge about the mechanisms of cancer and we made our case in a responsible and not over-promising way."

In 1971, "We felt that a little money would cure everything but now we realize that it hasn't and it's going to be a long and hard struggle. Everybody back then was looking for a magic bullet," said A. Hamblin Letton, M.D., president of the American Cancer Society in 1971-1972 and now professor of surgery at the Medical College of Georgia.

During the tenure of Arthur Upton, M.D., as NCI Director (1977-1979), the National Cancer Program came under serious scrutiny. Impatient legislators questioned the pace of research while frustrated cancer patients bought into highly publicized unproven "miracle cures" such as laetrile.

"A number of people began arguing that we were not winning the war on cancer but losing it. I had to explain that the war on cancer should not be compared with the Vietnam War or the Manhattan project or the Apollo project, which it was being compared to at the time," said Upton, now director of environmen-

Dr. Arthur Upton

tal medicine at New York University School of Medicine.

Unlike those projects, in which a goal could be reached through established steps and timetables, the search for a cancer cure required a comprehensive understanding that was still elusive, and a broad-based approach—like putting together the pieces of a puzzle, he said.

Controversy Exploded

Meanwhile, the laetrile controversy exploded. Patients on NCI-supported clinical trials were obtaining laetrile on the side; many cancer patients mortgaged their homes for treatments in Mexico. Increasingly, state legislatures—over the objections of NCI and in the face of existing scientific evidence—began moving toward legalizing the substance.

"There was anecdotal evidence regarding the efficacy of laetrile but animal data, which couldn't be 100% predictive, didn't support it. A great deal of debate took place inside the institute and we finally decided to invest in a clinical trial, which yielded no [positive] results," Upton said.

While that finally "took the steam out of the laetrile movement," it came at the cost of a bitter battle with Congress and state legislators that evolved into a political rather than a scientific issue.

Questioning Success

In 1986, John Bailar, M.D., Ph.D., an NCI alumnus, published a paper in the *New England Journal of Medicine* questioning whether the war on cancer was a losing battle.

Publication of his piece sent ripples through the scientific and public policy communities—and has been the focus of controversy as well as the basis for some of the criticism of the cancer program ever since.

"The lesson I wanted to come across from our paper was: We'd better start getting serious about prevention," said Bailar, now at McGill University in Montreal.

NCI Revamped

At the time Bailar's paper was published, Vincent T. DeVita, Jr., M.D., was at NCI's helm. He had made major policy shifts toward prevention shortly after becoming director in 1980.

DeVita established the Division of Cancer Prevention and Control at NCI and had 38 chemoprevention clinical trials up and running before his departure. In addition, he gave the green light to develop the recently announced $135-million ASSIST program that aims to control tobacco use in a nationwide effort.

Dr. Vincent T. DeVita, Jr.

"Congress always complained that we were spending too little money on prevention while we were supporting half of all the molecular biology conducted in the U.S.," said DeVita, now at Memorial Sloan-Kettering Cancer Center in New York.

He added that it was difficult to convince them that the investment in basic biology was an investment in prevention that "is now paying off."

Today, ironically, segments of the growing cancer patient advocacy movement are pushing "as they did 20 years ago" for greater and faster strides in finding cures.

Since 1971, when the American Cancer Society dominated the political scene on patient concerns, more than 20 national and local "grassroots" patient groups have been established—most of them in the last 5 years—to vie for the attention of policymakers in successfully pursuing their political agendas.

Coalitions are evolving that represent the

interests of breast cancer patients, kidney cancer patients, children with cancer, as well as their families and friends. Other groups push for expanded insurance reimbursement as well as access to drugs, or for more federal dollars for cancer research.

And they have had some success. Women's health issues, for example, have moved to the front burner of the research agenda through efforts of an increasingly persistent and vocal advocacy movement.

Needs Revitalizing

Although during the 1970s the war on cancer was fueled with more money than any other disease, the 1980s brought a leveling of cancer appropriations. Today, NCI is "holding its own" relative to other federal research entities, according to congressional sources.

"It's a program that needs revitalizing," Lane Adams said, "and it should be a high priority on the part of all cancer concerns because the Washington political establishment will only react when hometown America brings pressure to bear on its legislators."

In the existing fiscal climate, although some view the bypass budget authority granted to NCI by the Act as a major asset, others dismiss it as a "perfunctory relic" that has little real value.

According to a House Appropriations Committee staff member, "never" has NCI's bypass budget influenced appropriations, nor are committee members likely to be swayed by the "emotional" appeals of cancer advocacy groups—especially in an era of greater budgetary constraints.

"The view that the bypass budget is the most important part of the appropriation process is nonsense," the staff member said.

Resist Earmarking

"Neither have we tried to set budget policy at NCI on emotional needs. The House side is constantly trying to resist earmarking funds for any particular sub-cancer; we [the appropriations committee] just decide on a total and then ask NCI how the money should be spent.

"Overall, there is congressional support for the cancer program, but still, there is impatience and frustration with the rate of progress. At close to $2 billion a year, this program is a large enterprise. It has had an enormous investment," the staff member said.

"While we don't have any short-term expectations or visions of magic bullets, people here feel this investment should produce some fundamental leaps forward in terms of prevention, treatment, or cure, and they expect it in a 25- to 30-year timeframe from when the Act was passed," the staff member explained.

Different Focus

In the early 1970s, however, things were different.

"Lawmakers did pay attention to the bypass budget because it freed people at NCI to talk about what was needed and communicate that to Congress," said Paul G. Rogers, who chaired the House Committee on Health and the Environment in 1971 and now practices law with the Washington, D.C., firm of Hogan and Hartson.

Paul Rogers

"It's true the president's budget is what [Congress] really looks at, but [the bypass budget] puts in an overall message what the Cancer Institute thinks this country should be doing and it's helpful to the lay public," Rogers added.

The administration of President George Bush advocates cancer research support in light of competing interests, according to the White House. His policy is to delegate budget decisions to cabinet-level officials while generally favoring an emphasis on prevention and cost-containment research.

"The whole notion of prevention is featured prominently in the president's budget. It is also

interesting to note that in a time when there is a finite, predetermined amount of resources, biomedical resources emerge a winner," said Hanns Kuttner, associate director for health and human services policy in the White House Office of Policy Development.

"The whole attitude toward the NIH in this Administration is that budgeting is a macro-level decision made at the Departmental level. How to divide the NIH pie has been and will be deferred to [Secretary of Health and Human Services] Dr. Louis Sullivan," Kuttner added.

Still, Kuttner points out that President Bush's personal physician, Burton J. Lee., M.D., is an oncologist and that the president lost a daughter to cancer. He also mentions that Vice President Dan Quayle's wife Marilyn is active in breast cancer concerns.

War Expanding

In spite of the controversies, the war on cancer is widening. And cancer policy development is expanding into state and local domains.

"We've been seeing a gradual shifting of cancer policy from the federal government to states and localities. This is especially true in areas such as reimbursement, regulation, and tobacco," said Connie Thomas, a policy analyst with the Intergovernmental Health Policy Project in Washington, D.C.

Two states currently mandate insurance reimbursement for off-label prescription drugs; 38 states and the District of Columbia have passed mammography quality and/or reimbursement legislation; California has established an expanded tobacco product tax to fund smoking cessation and prevention programs; and many localities are trying to ban cigarette vending machines from restaurants, taverns, and other public gathering spots.

She predictsthat this trend is likely tocontinue.

Today, the war on cancer is increasingly being waged as a multidimensional fight. Poverty, illiteracy, behavior, and the lack of access to care are rising to the forefront as issues that must be addressed before cancer research discoveries can be fully implemented.

"What we have to concentrate on in the 1990s is applying the knowledge that we already possess regarding cancer prevention, control, and treatment," said Harold Freeman, M.D., chairman of the President's Cancer Panel and director of surgery at Harlem Hospital.

"There is a challenge—even an imperative—to see that the results of our research benefit all Americans," said NCI Director Samuel Broder, M.D.

Renewed Commitment

"The burden of implementing all the provisions of this Act is simply beyond what NCI alone can do," Freeman added.

He called for a renewed commitment among the American people to wage the cancer battle over the next 20 years along with a coalition of federal government entities including the Departments of Labor, Housing and Urban Development, Agriculture, and Education; all federal health agencies; and more support from the legislative and executive branches.

"It's not acceptable that there are 37 million uninsured Americans who are not really benefiting from this war. Then there are the poor, with substandard living conditions, not enough education, poor nutrition, and unemployment that is amplified by lack of access to care," Freeman said.

"We are developing new strategies to wage this war," Freeman maintained. "Although we should celebrate and be proud of the strides we've made, it's no time to stop and rest on our laurels."

NATIONAL CANCER INSTITUTE